THE ÆTIOLOGY OF COARCTATION OF THE AORTA

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KNOWLEDGE of the causes of congenital malformations of the heart is still very incomplete. In 1955 we tried to extend this knowledge by inquiries about the families of 384 patients with such malformations, which were mostly Fallot's tetralogy (Polani and Campbell 1955). It would have been better if the group had been homogeneous, and more recently (1960) we have applied the same methods to 261 patients with persistent ductus arteriosus.

We here continue the inquiry among 151 patients with coarctation of the aorta. Campbell and Bayliss (1956) reported 130 of these but, because they were dealing with the course and prognosis, they omitted 7 others with additional cardiac malformations. We have included all these, and also another 14 who have been seen since. The age and sex distribution of these 151 patients is given in table I.

TABLE I—AGE-DISTRIBUTION (WHEN FIRST SEEN) OF PATIENTS WITH COARCTATION

Age (yr.)	0 to 9	10 to 19	20 to 29	30 to 39	40 to 49	50 and over	Total
Males..	20	36	24	13	2	0	95
Females	13	21	12	7	0	3	56
Total..	33*	57	36*	20*	2	3*	151

* There were 6 patients with aortic stenosis, aged 9, 21, 23, 31, 33, and 58 years.

Other Malformations in the Propositi

Malformations Known to be Associated

The association of coarctation wtih aortic stenosis, aortic regurgitation, and other abnormalities of the aortic arch, including persistent ductus, is now well recognised. Medial degeneration of the aorta, and berry aneurysms of the cerebral vessels, can be regarded as congenital vascular disorders, since the aorta may rupture in or even before the third decade (and did so in 2 of our patients, aged 20 and 22), and the rupture of berry aneurysms may lead to early death from intracranial hæmorrhage. 2 of our patients, aged 8 and 27, have died from intracranial hæmorrhage, probably from rupture of a berry aneurysm, and 4 others have recovered completely or partially from this. All these additional malformations were found in our series more often than would be expected by chance, and so were other malformations of the heart.

6 of our 151 patients had aortic stenosis that was non-rheumatic. The 3 over 30 had calcification of the aortic valve, as is generally found above this age. In the only 1 who came to necropsy there were two large aortic cusps and one small one. Bacon and Matthews (1959) have brought forward evidence to support the view expressed by Peacock, a hundred years ago, that bicuspid valves are likely to become stenosed.

A quarter of the patients had aortic regurgitation, including 4 of those with aortic stenosis. In the few necropsies, this was generally, but by no means always, associated with congenital bicuspid valves. Major abnormalities of the branches of the aortic arch were known to be present in 5 patients, and minor ones in some others. There were 7 with persistent ductus arteriosus, but in some series the proportion has been as high as 10%.

Other Malformations of the Heart

In addition, 12 of the 151 patients had some other malformation of the heart. 4 were cyanotic; 1 with Eisenmenger's complex (Campbell and Cardell 1953), 1 with transposition of the great vessels, 1 with tricuspid atresia, and 1 with Fallot's tetralogy. In the last the coarctation was trivial; in the other 3 it was quite severe. But they were not included because they presented with gross cyanosis and not as cases of coarctation.

Of the 8 acyanotic patients, 1 had slight pulmonary-valve stenosis, 1 had moderate pulmonary infundibular stenosis, 1 was thought to have a ventricular septal defect, 1 had a pulmonary vein draining into the superior vana cava. No less than 3 were thought to have congenital mitral regurgitation, and in 2 of them this led to atrial fibrillation before the age of 20. The 8th developed atrial fibrillation when she was 16, and this led to the discovery of slight mitral stenosis, slight coarctation, and bilateral superior venæ cavæ with a pulmonary vein draining into the right one. In the last patient (excluded because of her multiple lesions), and in a boy with mitral regurgitation and fibrillation, coarctation was found only after careful examination in hospital, but in the other 6 it was the most important lesion.

This incidence of 8% for other cardiac malformations is twelve times more than would be expected by chance, if we accept the incidence of all congenital heart-disease among the general population of infants at birth as 0·6% (Carlgren 1959). In our similar study of persistent ductus, such patients were excluded by definition, but perusal of the case-notes suggests that the incidence would have been about 10%.

Non-cardiac Malformations

Most patients with coarctation are so well and of such good physique that we were surprised to find 19 examples of non-cardiac malformations. 13 patients had major malformations, of which the first 11 cases (1–11) were certainly congenital and the next 2 cases (12 and 13) were probably congenital; the last 6 (cases 14–19) had less severe malformations.

CASES 1 to 3.—3 patients had Turner's syndrome and gonadal dysplasia. All had broad webbing of the neck which is always found when Turner's syndrome and coarctation are associated. All 3 had the usual appearance and characters of females, but they were male chromosomally.

CASE 4.—A girl had a lymphomatous swelling of the legs that had been mistaken for congestive heart-failure, ptosis of the left eyelid, and possibly Turner's syndrome.

CASE 5.—A boy had a minor degree of status Bonnevie-Ullrich.

CASE 6.—A man had had a successful operation for hypospadias in infancy.

CASE 7.—A boy had been successfully treated for club foot.

CASE 8.—A girl had had an operation for bilateral congenital cataract in infancy.

CASE 9.—A girl had perception deafness and a large goitre.

CASES 10 and 11.—2 patients had some degree of mental defect: the boy had also idioglossia, and the girl icthyosis.

CASE 12.—A man, aged 27, had had colectomy for (? familial) polyposis of the colon; the findings in his family are described later.

CASE 13.—Another man had a curious eye condition which started when he was 18 with temporary attacks of blindness in either eye: at 26 one of these blind areas became permanent, and at 32 he had optic atrophy on the right, and a large scotoma below the fixation point.

CASE 14.—A woman had bilateral cervical ribs.

CASE 15.—A boy had an operation for squint.

CASE 16.—A boy had extreme myopia, regarded as congenital.

CASE 17.—A boy, aged 14, had been given thyroid for years for juvenile myxœdema, but he remained well when it was stopped.

CASE 18.—A man had undescended testicles, and had had an operation for congenital torticollis.

CASE 19.—A girl had had a nævus removed from her head and a lipoma from her neck.

Finally, a girl who had been deaf and semimute from birth was excluded because her mother had rubella during the 3rd month of pregnancy—the only example of this in the series.

Even if we omit the 6 minor malformations and the 2 that were probably congenital an incidence of 11 major malformations (7%) in our 151 patients is more than would be expected by chance. Furthermore, this is a minimal figure because our series included very few infants, and among these there would certainly have been some with major defects that could have proved lethal before coarctation was diagnosed. We have not found many similar studies of patients with coarctation, but Lamy et al. (1957) found that 7% of their 54 patients had also some non-cardiac malformation—an incidence lower than in most of their other groups with congenital heart-disease. MacMahon et al. (1953) also found a great increase of other malformations among subjects with congenital heart-disease (15%, excluding another 6% with mongolism), and the proportion was higher among those with coarctation (8 of the 32 cases, including 3 with skeletal malformations).

Malformations in Sibs of Propositi

We had lost touch with some of the 151 patients, and excluded those who had cyanotic heart-disease as well as coarctation, and those who were not of British stock. Questionnaires sent to 119 patients were filled up in all or most particulars by 109 (92%) 2 sisters in one family had coarctation, and 1 woman had been adopted and knew nothing about her family, so this left us with a hundred and seven families. We think that the replies can be taken as coming from a representative series of hospital and private patients with coarctation.

More than one family in each seven reported some congenital malformation, sometimes in more than one member. Malformations of the heart were not specially common, being found in only 5 instances.

Cardiac Malformations in Sibs

There was only one example of cardiac malformation—2 sisters who had coarctation of the aorta. In both it was severe, and both did well after surgical treatment (Campbell 1959).

This incidence of 0·4% among 252 sibs is much lower than among the sibs of our patients with congenital heart-disease in general (1·4%), with persistent ductus arteriosus (2·1%) (Polani and Campbell 1955, 1960), or with pulmonary stenosis (2·2%) or atrial septal defect (0·8%) (unpublished data). In most of them both sibs had the same malformations, and this was so in our present example. Lamy et al. (1957) found an example of coarctation and another of Fallot's tetralogy among the sibs of their 54 patients with coarctation. McKeown et al. (1953) found no such examples, but the numbers were small; for propositi with all forms of congenital heart-disease they found 1·8% of the sibs born later had congenital heart-disease.

Non-cardiac Malformations

There were 7 major non-cardiac malformations among the 252 sibs, in 6 sisters and 1 brother:

A sister had congenital dislocation of the hip.

A sister died in infancy with spina bifida.

A sister died at 5 months with œsophageal stenosis.

A sister died with a " tumour of the spinal cord " when about 20.

A sister, aged 5 years, died after operation for a cerebellar medulloblastoma.

A sister had been born with a " partial undeveloped child attached to her back ".

A brother had spastic diplegia.

This incidence of 2·8% is rather more than we found in our persistent ductus series (2%), and for such major malformations it is probably more than would be expected by chance. It is curious that of the 8 sibs with cardiac or non-cardiac malformations, 7 should be sisters and only 1 a brother, for this would happen by chance only once in 128 trials. We do not think, however, that sisters are really more likely than brothers to have congenital malformations. Lamy et al. (1957) found the incidence of non-cardiac malformations was 1% in the sibs of their propositi, and this was the same as the incidence in their control series. McKeown et al. (1953) also found the incidence of all non-cardiac malformations in the sibs to be 0·9%—i.e., no more than might be expected by chance.

Malformations in Parents and Children of Propositi

Malformations in Parents

Only 1 parent in these 107 families was known to have congenital heart-disease—a mother who had a persistent ductus. Only 1 reported a non-cardiac malformation—a mother who had been born with a large goitre. Lamy et al. (1957) found no congenital heart-disease among the parents of their 54 cases of coarctation.

In addition, 2 fathers in our series (and especially the 2nd) might have had coarctation. 1 died with an enlarged heart when he was 34, and there was no known rheumatic history. The other died when 73, with congestive heart-failure, hypertension, and aortic regurgitation—findings suggestive of coarctation. On inquiry at the hospital, this had not been diagnosed, but neither had it been excluded by palpation of the femoral pulses. The patient's brother was attending another hospital with hypertension: he had no signs of coarctation but our inquiries led to the physician detecting an aortic diastolic murmur. The presence of aortic regurgitation in the father and brother of our patient with coarctation (himself without aortic regurgitation) might be explained by the presence of bicuspid aortic valves.

13 fathers and 6 mothers had died, 7 from heart-disease (including 5 from cardiac infarction between the ages of 53 and 69, and 2 from rheumatic heart-disease), 5 from cancer, and 6 from other causes—much as might be expected. 6 others gave a history of rheumatic fever. There were several cases of heart-disease in at least four families but no reason to think that it was other than coronary or hypertensive. In one family, for example, where several members with heart-disease were reported, the patient's grandmother " after being out hunting all day and entertaining a large party to dinner, died in her sleep that night ". All these are, we think, no more than might be expected by chance.

Malformations in Children

Many of the propositi were too young to be married so that there were not many children. We know about twenty-five families (many probably not completed) with 49 children (26 boys and 23 girls). But even in this small number, there were 2 with malformations. The son of a woman with coarctation had pulmonary valvular stenosis, and the son of another had a cleft palate and hare-lip.

Finding 1 mother with a ductus and 1 with a goitre is not significant among 214 parents. 1 boy with a cleft palate and 1 boy with pulmonary stenosis among 49 children of patients with coarctation is more likely to be significant.

Families with two or more examples of congenital heart-disease have been reported on many occasions, but not very often for coarctation of the aorta. Taylor and Pollock (1953) reported a family where the mother, her son, and her daughter all had coarctation (proved by necropsy in the son). They could not find many other examples but mentioned the case of a father and son with coarctation (Walker 1934) and 2 pairs of brothers all with coarctation (Klemola 1939). Since then, Moss (1955) has reported a brother and sister (9 years younger) both of whom had successful operations for coarctation: the 2nd boy, born between these two, had bilateral congenital cataract, but none of the 3 had a history of maternal rubella or other infections during pregnancy. Wood (1956) has reported the case of a woman with coarctation, whose brother had coarctation and died from cerebral hæmorrhage, aged 17, and whose cousin had coarcta-

tion and died from rupture of an aortic dissecting aneurysm. We have added the example quoted above of 2 sisters with coarctation.

Malformations in other Relatives

Cardiac Malformations

There were only 2 examples—a cousin of a father had a daughter with congenital heart-disease who died soon after she was 20, and a cousin of a mother had a " blue baby " who was a total invalid and died at 20. Lamy et al. (1957) found no cousins of their patients with coarctation who had congenital heart-disease, though they did in some other groups.

Non-cardiac Malformations

In uncles, aunts, or first cousins.—1 mother's sister died when 4 weeks old with hydrocephalus. 2 sibs of the father were born malformed: 1 had only one eye and died in infancy, and 1 with hydrocephalus died aged about 5 years. A first cousin had a club-foot, another first cousin had an abnormal great toe, and 2 first cousins were mentally defective. A brother's son had had an operation for imperforate anus, and a sister's son had needed treatment for a stenotic or imperforate anus; the patient himself had polyposis of the colon, which is generally familial, though the only hint was that his grandmother had died with " carcinoma of the rectum ".

In less close relatives.—2 brothers, first cousins of the mother, were born with congenital pyloric stenosis. A first cousin of the mother was born with a twisted leg that had had to be amputated below the knee in infancy. A child of a first cousin was under observation with congenital hypoplastic kidneys. 5 other cases are excluded because we were not certain that the heart lesions were congenital rather than rheumatic, but it seems likely that some of these may have been congenital.

We cannot express any opinion about the incidence because we do not know the numbers at risk, but there were known to be malformations in 3 uncles or aunts, in 4 first cousins, in 3 nephews, and in 4 other less close relatives.

Consanguinity of Parents

An unusual number of consanguineous marriages among the parents would support inheritance as a recessive Mendelian, character. There was, however, no consanguinity of the parents or of the grandparents of our propositi with coarctation: a hundred and one of the families answered this question for their parents, and all but 3 of these for their grandparents also. 2, however, added comments about consanguinity further back. In one of these the mother's maternal grandfather and paternal grandmother were first cousins, but this was the case where the mother had rubella in the first three months of the relevant pregnancy. In the other the maternal grandfather's parents were first cousins. Lamy et al. (1957) found no first cousins and only 1 pair of second cousins among the parents of their patients with coarctation, though they found this more often in most other groups of patients with congenital heart-disease. There is, therefore, no direct evidence in favour of coarctation as a whole, or even of a subgroup of it, being inherited as a recessive Mendelian character.

The Influence of Parental Age and Birth Order

The age of the parents did not obviously differ from what might be expected. In the 105 mothers where we had the information the mean of their ages at the time the affected child was born was 28·54 years, and this is not far from the expectation in the general population. Penrose (1955) thinks that the difference between mean paternal and maternal ages is in some ways a more useful measurement, and that when the paternal age is increasing unduly it suggests the possibility of a " failure to copy genes correctly " because of the larger number of cell divisions in the male germ-line. We know the ages of both parents in 101 pairs; and means were 31·34 years for the fathers and 28·47 years for the mothers. The mean age of the fathers is 0·44 year greater than that given by Penrose (1955) for the general population, and the mean difference of paternal and maternal ages is 2·87 years as compared with 2·3 years for the general population in England. In our cases of persistent ductus arteriosus we found this difference was 3·3 years; so in both there is some evidence that genetic factors may be important.

Any correlation between maternal age and congenital malformation is often thought to show that the cause of the malformation is environmental, but equally it may be the factor that reveals a genetically determined defect. The association between maternal age and mongolism, and between mongolism and congenital heart-disease, which is found in 18–50% of mongols (Berg et al. 1960), make maternal age worth investigating in congenital heart-disease.

The maternal ages at the time of birth of the propositi with coarctation may be compared with (1) a matched control population, (2) the data of the Registrar General for the general population, or (3) the ages at the time of birth of the normal sibs of the propositi. The first method is ideal for comparing children with some malformation born in a particular period and locality with all other children born in this period and locality, but it is difficult to apply to children born in different social groups, in different areas, and over a period of several decades. This last point also makes comparison with the Registrar General's data rather difficult to interpret. We have, therefore, used the third method. Granted certain assumptions it can be taken to supply an internal control group. It is most accurate when the families studied are complete: considering the age of many of our patients with coarctation most families were complete, but not all of them, which introduces some error.

Birth order is another variable that can influence abnormalities in the offspring. For instance, conditions dependent on immunological sensitisation of a mother to her fœtus can clearly be related to birth order, and the quality of gestation itself can be different at the extremes of a large family. The influence of birth order can be studied by the same three methods, but in view of its close correlation with maternal age, means have to be devised for separating the respective influences of these two possible factors. Pearson's method, which assigns the probability of an affected child being born in the first, second, or *n*th place in the family in direct proportion to the total number of children and places, is known to give incorrect results by overestimating the proportion of affected first-born children (Penrose 1934a). The expectation of an affected child being born at any given place in the family must depend on the size of the family (Greenwood and Yule 1914), and this method has been developed and used by Penrose (1934b, 1946, 1949) in various malformations of the nervous system.

The method used in our investigation is based on the work of Greenwood and Yule, and of Penrose. A series of tables was compiled showing the number of maternities, the birth rank, and the maternal age (in five-year periods) for each family. From this, a table was calculated showing the observed and expected numbers for each parity and for each maternal age, and the sampling variance. The results are shown in detail in table II, and in shorter and simpler form in table III.

Neither maternal age nor birth order appear to influence the origin of coarctation of the aorta, as in no instance is there significant difference (greater than twice the square root of the sampling variance) between observed and expected numbers of affected subjects. There were 2 more propositi than would be expected born to mothers of 24 or under (30 instead of 28) and 2 less than would be expected born to mothers aged 30–34 years (21 instead of 23), but these small differences are not significant. Nor did birth order have any significant influence. There were 2 more first-born children (43 instead of 41), 2 more second-born (28 instead of 26), and 1 more sixth-born and later (7 instead of 6): against this, at the two extremes, there were 3 less third-born (15 instead of 18) and 2 less fourth-born (6 instead of 8).

We had thought that coarctation was more common at the end of a large family when the mother was getting older—e.g., the last of 10 children born when the mother was 46, the last of 6 children born when the mother was only 35, and the last of 5 children born when the mothers were 40, 37, and 35 respectively. But there were many exceptions. Further data on this aspect are worth collecting, but in the absence of any statistical

TABLE II—COMPARISON OF 104 PATIENTS WITH COARCTATION, AND THEIR SIBS, WITH RESPECT TO MATERNAL AGE AND BIRTH ORDER

Birth order	Maternal age (yr.) Under 19	20–24	25–29	30–34	35–39	40 and over	Total
1st	**2** 4 1·70±0·52*	**17** 50 18·39±8·96	**15** 28 14·04±4·69	**6** 9 3·65±1·67	**3** 4 2·83±0·47	**0** 1 0·50±0·25	**43** 96 41·11±16·56
2nd	**1** 2 0·37±0·30	**9** 21 6·22±3·79	**12** 32 10·79±6·77	**3** 15 4·47±2·98	**0** 6 2·36±1·35	**3** 4 1·83±0·97	**28** 80 26·04±16·16
3rd	..	**1** 7 1·44±0·84	**5** 27 6·88±4·93	**7** 24 7·53±4·88	**2** 5 1·70±1·08	**0** 2 0·66±0·44	**15** 65 18·21±12·17
4th	..	**0** 2 0·37±0·30	**3** 12 2·39±1·85	**1** 18 4·07±3·21	**2** 5 1·23±1·06	**0** 1 0·20±0·16	**6** 38 8·26±6·58
5th	..	..	**0** 7 1·06±0·89	**2** 8 1·52±1·20	**3** 10 2·04±1·46	**0** 2 0·40±0·48	**5** 27 5·02±4·03
6th and over	..	..	**1** 1 0·17±0·14	**2** 11 1·80±1·46	**2** 11 1·75±1·45	**2** 14 2·25±1·71	**7** 37 5·97±4·76
Affected and total	**3** 6	**27** 80	**36** 107	**21** 85	**12** 41	**5** 24	**104** 343
Expected affected and variance	2·07±0·82	26·42±13·89	35·33±19·27	23·04±15·40	11·91±6·87	5·84±4·01	104·61±60·26

* The three sets of numbers represent: (1) the number of affected children (in heavy type), (2) the total number of children at a given rank and maternal age-group, and (3) the expected number of affected children with the sampling variance of this estimate.

evidence in our sample and with our method, our impression was not substantiated. We concluded that neither maternal age nor birth order influence significantly the production of coarctation of the aorta.

Twins

Twinning does not seem to be of special importance. There were 5 pairs of twins in these hundred and seven families: 1 pair of almost certainly identical twins, and 4 dizygotic pairs. Of the identical twin girls, one had coarctation and the other was normal: this may seem surprising, but it has been found in most cases of congenital heart-disease in identical twins (Uchida and Rowe 1957, and our own experience). In the 2nd pair, 1 had coarctation and his brother was normal; and in the 3rd, born at 7 months, one had coarctation and his brother died after 12 hours, but we do not know if he had heart-disease. The other 2 pairs were all normal boys born in the families of those who had coarctation.

TABLE III—DISTRIBUTION OF CASES OF COARCTATION ACCORDING TO MATERNAL AGE AND BIRTH ORDER

Birth order	Maternal Age (yr.) Up to 24	25–29	30–34	35 and over	Total
1st	19 (*20·0*)†	15 (*13·9*)	6 (*3·7*)	3 (*3·3*)	43 (*41·1*)
2nd	10 (*6·5*)	12 (*10·7*)	3 (*4·5*)	3 (*4·2*)	28 (*26·0*)
3rd	1 (*1·4*)	5 (*6·9*)	7 (*7·5*)	2 (*2·3*)	15 (*18·1*)
4th	0 (*0·4*)	3 (*2·4*)	1 (*4·0*)	2 (*1·4*)	6 (*8·2*)
5th	..	1 (*1·2*)	2 (*1·5*)	3 (*2·4*)	5 (*5·0*)
6th and over	..		2 (*1·8*)	4 (*4·0*)	7 (*6·0*)
Total	30 (*28·3*)	36 (*35·1*)	21 (*23·0*)	17 (*17·7*)	104 (*104*)

† The figures in parentheses indicate the " expected " number of cases.

Seasonal Incidence of Births

Because more girls with persistent ductus arteriosus were born from August to October and fewer from December to March (Polani and Campbell 1960), and because seasonal variations of births have been reported in other congenital anomalies, such as anencephaly (McKeown and Record 1951, Edwards 1958) and congenital dislocation of the hip (Record and Edwards 1958), it seemed worth analysing the seasonal incidence for another malformation. More girls with coarctation were born in September and October and fewer in February and March (and May and June), but the numbers were very small. The boys showed an opposite trend, so that when they were combined the differences were reversed, the peak of births being in March and April and the nadir in August and September (table IV). The monthly figures are too small to be significant, and we report them only so that they may be added to others.

If we take the conventional quarters and combine the sexes, the numbers are larger but the differences are smaller. Then 32% of the boys were born in the first quarter, and 31% of the girls in the last quarter of the year, instead of the more equal distribution in each quarter. Normally, the birth-rate is a little higher in the second quarter of the year, but births were disturbed during and after the recent war. We have, therefore, taken the birth dates of the 226 sibs of our propositi as a more valid comparison. Our patients with coarctation showed the greatest excess in the first quarter of the year (27·9 instead of 23·0%), and a deficiency or balance in the other three-quarters 25·2 instead of 28·0% in the second, 22·6 and 22·5% in the third, and 24·3 and 26·5% in the fourth quarter, but these differences are not great.

The difference is greatest if, instead of the conventional quarters, we take four months together. Then the number of patients with coarctation born between December and March is 42, between April and July 40, and between August and November only 29 (table V). This difference is entirely due to the larger number of boys born in the first two periods, the figures being 30, 27, and 12 respectively. There is no such difference in the sibs of our patients, boys or girls, the figures being 70, 82, and 74 respectively.

We think these differences are real though they must be confirmed by a larger series. Both in coarctation and in persistent ductus, there seems to be some effect of season on the number of births in the sex that is most prone to the malformation (boys with coarctation and girls with persistent ductus), though the time of year is different in the two cases. Even if the facts of seasonal variations in the births or conceptions of different malformations are established, no satisfactory explanation is at hand.

Sex Incidence in Coarctation

Nearly all series agree that coarctation is more prevalent in males, sometimes by as much as 4 to 1, but 2 to 1 or less in more recent series. Of our cases, 63% were male and 37% female (1·7 to 1). No doubt the male preponderance has been exaggerated because there are more medical examinations of men

TABLE IV—SEASONAL INCIDENCE OF BIRTHS (BY MONTHS) OF PROPOSITI WITH COARCTATION, AND OF THEIR SIBS

—	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
Boys with coarctation	7	4	11	8	6	5	8	4	2	2	4	8	69
Girls with coarctation	5	2	2	5	2	2	4	3	4	6	4	3	42
Total	12	6	13	13	8	7	12	7	6	8	8	11	111
Brothers	4	8	10	12	10	13	10	8	9	11	17	11	123
Sisters	10	11	9	11	6	11	9	8	7	8	6	7	103
All sibs	14	19	19	23	16	24	19	16	16	19	23	18	226

for army service, life assurance, &c., for most cases have been missed at the school medical examination in the past, though this should not be in a condition that can be diagnosed so easily by feeling the femoral pulse.

In our series the male/female ratio did not change significantly in the first four decades taken separately, and for all older patients taken together, because of the smaller numbers. The ratio was always between 1·5/1 and 2·0/1, as can be seen from the figures given in table I. There is, therefore, no evidence of a higher mortality-rate among girls or women to account for the male preponderance, though our data do not exclude a higher prenatal or neonatal female mortality.

It is tempting at times to speculate beyond the evidence—here to try and explain the higher incidences of coarctation in boys and of persistent ductus in girls. Although coarctation is generally accepted as prenatal in origin, another hypothesis has been put forward to explain it. This suggests that the muscle responsible for immediate closure of the ductus after birth, so preparing the way for the subsequent fibrous closing, may spread beyond the ductus into the aorta, and, by undergoing the same changes, may lead to narrowing of the aorta—i.e., coarctation (Bonham-Carter 1954).

Assuming that " maleness " encourages the development and contraction of this muscular tissue and that " femaleness " discourages it, then boys would be more likely to develop coarctation and girls a persistent ductus, though no doubt the inherent qualities of this muscular tissue would influence the likelihood of these changes. The different seasonal incidence of these two conditions could then be partly explained. In our series, more patients with coarctation were born from December to July, the difference being entirely due to the boys, and more patients with persistent ductus from August to October, this being entirely due to the girls. This might be expected if the environmental factors influencing the children born from December to July were more likely to encourage the male tendency to development and contraction of this muscular tissue, and those influencing the children born from August to October were less likely to encourage it. But all this is pure speculation.

TABLE V—SEASONAL INCIDENCE OF BIRTHS OF PATIENTS WITH COARCTATION AND THEIR SIBS (SUMMARISED)

—	Total no.	Period of births		
		Dec. to March	April to July	Aug. to Nov.
Boys with coarctation ..	69	30	27	12
Girls with coarctation ..	42	12	13	17
Total	111	42	40	29
Brothers	123	33	45	45
Sisters	103	37	37	29
All sibs	226	70	82	74

Birth-weights and Coarctation

The 32 girls with coarctation were lighter at birth than would be expected, although the 54 boys were of normal weight. This is true whether one takes the mean weight at birth, which was 7·70 lb. for the boys and 6·52 lb. for the girls, or the weight distributions (see table VI). The difference is well shown by taking the proportion with unusually light or heavy birth-weights. Of the girls 25% weighed $5^1/_2$ lb. or less and none were over $8^1/_2$ lb., the corresponding figure for their normal sisters being 9 and 12%. Of the boys, only 7% weighed $5^1/_2$ lb. or less, and 26% were over $8^1/_2$ lb.—figures that did not differ greatly from those for their normal brothers (5 and 22% respectively). Normal boys are a little heavier than girls, but the average difference is only 0·2 lb. against the 1·18 lb. of our patients with coarctation, which is six times as much.

In the absence of an appropriate control population, we have compared these weights with those of their 102 normal brothers and 93 sisters; this eliminates any factor of selection of social groups or different ecomonic conditions. As weight at birth increases with birth order, we compared separately the affected boys with those born before and those born after them, and dealt with the girls in a similar way. The mean weights of the boys born before and after were 7·94 and 7·60 lb. respectively, and of the girls 7·42 and 7·22 lb. respectively. It should be noted that, contrary to expectation, the normal sibs born before are heavier than those born after, though the differences are not significant. It seems legitimate to combine the weights for the sibs born before and after for comparison with the weights of the propositi because we have shown that coarctation is not related to birth order.

TABLE VI—DISTRIBUTION OF BIRTH-WEIGHTS OF 86 PATIENTS WITH COARCTATION AND 195 OF THEIR NORMAL SIBS

Weight (lb.)	Patients with coarctation		Normal sibs	
	Girls	Boys	Girls	Boys
2·6–3·5	1	..	..	..
3·6–4·5	4	..	2	2
4·6–5·5	3	4	6	3
5·6–6·5	7	11	15	14
6·6–7·5	10	15	37	34
7·6–8·5	7	10	22	27
8·6–9·5	..	8	8	14
9·6–10·5	..	5	2	5
10·6–11·5	..	1	1	1
11·6–12·5	..	..	..	2
Total no.	32	54	93	102
Mean (lb.)	6·52±0·25	7·70±0·19	7·36±0·13	7·78±0·14
Mean (kg.)	2·96	3·50	3·35	3·54
Standard deviation	1·44	1·44	1·25	1·44

The mean birth-weight for the girls with coarctation was only 6·52±0·25 lb., compared with 7·36±0·13 lb. for their normal sisters—a highly significant difference. On the other hand, the mean weight for the boys with coarctation was 7·70±0·19 lb. compared with 7·78±0·14 for their normal brothers—figures that show no significant difference. In a similar series of patients with persistent ductus arteriosus we found no significant difference for either girls or boys (Polani and Campbell 1960). In both these analyses we have omitted patients born after maternal rubella, and those who were twins because these often affect birth-weights.

One reason for the light weight of the girls is apparent. 3 of our patients had Turner's syndrome (birth-weights 3·5, 5·0, and 6·0 lb. with nothing significant about the birth-weights of their sibs). In this condition, particularly in the chromatin-negative subject, birth-weight is generally low (Polani, personal data), as 2 of our 3 patients demonstrate, though this lowering of birth-weight does not appear striking in some of the reported series. It is reasonable that in this condition, with multiple anomalies related to a chromosomal change, the growth of the fœtus should be impaired. If we remove from our series those with Turner's syndrome, the average birth-weight of the remaining girls is 6·69±0·24 lb., a little higher than before but still significantly less than that of their normal sisters. The other 6 girls with a low birth-weight did not seem in any way unusual; they included 2 of excellent physique, 1 of whom was perhaps the best-looking girl in the series (4·5 lb. at birth). It seems most unlikely that any of these were undiagnosed cases of Turner's syndrome. Nor were the boys with a low birth-weight remarkable in any other way. In 2 of these families all the children had low birth-weights but in the others they were average.

The association of Turner's syndrome with coarctation can explain only a small part of the unusually light mean birth-weight of the girls with coarctation. In girls, but not in boys, there seems to be a general retardation of fœtal growth, but the reasons for this are not clear and the size of our sample does not warrant further speculation.

Stillbirths and Miscarriages

Murphy (1947) thought that stillbirths, miscarriages, and premature births were observed more often before the pregnancy resulting in the birth of a malformed child. In a large series one sees examples of this, but we (Polani and Campbell 1955) could not find any evidence of a relationship, and we thought the miscarriages were distributed as would be expected by chance in their 384 patients, mostly with Fallot's tetralogy.

We have made the same inquiries in this series, and in the hundred and seven families with 357 children there were 4 stillbirths and 22 abortions or miscarriages recorded, and another 8 children died in infancy. This does not seem an unduly high proportion, and they did not seem to be related in time to the births of the children with coarctation. We do not know how complete these records are, but all the patients were asked to include stillbirths and miscarriages and several did so while others said there had been none.

Conclusions

Patients with coarctation of the aorta are recognised to have aortic regurgitation, congenital aortic stenosis, a persistent ductus, cerebral aneurysms, and medial degeneration of the aorta more often than would be expected by chance. In addition, other congenital malformations of the heart were found in 8% of our 151 patients.

Although so many are of good physique, they are more likely to have other congenital malformations also. These were found in at least 8% of our series: Turner's syndrome was the most common, and there were examples of hypospadias, club-foot, and mental and ocular defects.

Among the 252 sibs of our propositi there was only 1 sister with a congenital heart-lesion—coarctation—but there were 6 sisters and 1 brother with non-cardiac malformations. 3% with major malformations is much less than was found among the propositi, but probably more than would be expected by chance. Among the 45 children of patients with coarctation there were 2 boys with major malformations, again more than would be expected by chance, but the numbers are small. This was not true for the parents of the propositi, however, for among the 214 mothers and fathers there were only 2 mothers with malformations, which is no more than would be expected by chance. There were known malformations in 18 other relatives, but here the number at risk is not known. In all these groups the malformations were of many varied types, and no one type predominated.

There was no consanguinity of the parents or grandparents. There was, therefore, no evidence of inheritance as a recessive Mendelian character. There was no special incidence of twins in these families.

Mean paternal age exceeded mean maternal age by 2·87 years, which is significantly more than normal (2·3 years), and is said to favour a genetic cause. Maternal age and birth order had no significant influence on the incidence of coarctation. It seemed to be rather more common towards the end of a large family as the mother was getting older, but this was not statistically significant. There was only 1 case where the mother had rubella during the early months of the relevant pregnancy, and no other obvious infections or environmental causes were found.

Boys with coarctation (but not girls) were born more often from December to July, and especially in March and April. This contrasts with persistent ductus, where girls (but not boys) are born more often from August to October.

The birth-weights of boys with coarctation did not differ significantly from their normal brothers (7·70 against 7·78 lb.). On the other hand the girls were much lighter (6·52 against 7·36 lb.). Although the numbers are small (32) the difference is highly significant. It is explained only partially by the association with Turner's syndrome, and the difference is still significant if these patients are excluded. Stillbirths and miscarriages did not seem to be related to the birth of patients with coarctation.

As in most series, the incidence was higher in males, 95 to 56, or 1·74 to 1. This ratio was about the same in each decade, and so the difference is not due to a higher female mortality-rate in childhood or adult life, though it could be due to a higher mortality in the prenatal or neonatal periods.

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RELATION OF EYE SIGNS IN GRAVES' DISEASE TO CIRCULATING ANTIBODIES TO THYROGLOBULIN

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AUTOIMMUNE reactions have been demonstrated in Hashimoto's disease (lymphadenoid goitre) and to a lesser extent in other thyroid diseases, including thyrotoxicosis (Doniach and Roitt 1957, Mackay and Perry 1960). In addition, lymphocytic infiltration has been described in the thyroid glands of patients with thyrotoxicosis (Simmonds 1913, Troell 1923), though this is not as pronounced as in Hashimoto's disease. Lymphocytic infiltration has also been found in the ocular muscles of patients with exophthalmic Graves' disease (Dudgeon and Urquart 1926).

Lymphocytic infiltration in patients with Graves' disease and Hashimoto's disease may be related to similar immunological responses in both conditions; and Roitt and Doniach (1960) suggested that immune reactions may be related to the eye signs in Graves' disease. We have studied the relation between antibody titres to thyroglobulin and the eye signs of Graves' disease.

Methods

Case Selection

Every patient had Graves' disease with at least two of the three classical signs (exophthalmos, goitre, and hyperthyroidism). The hyperthyroid state was confirmed

TABLE I—T.R.C.H. TITRES IN SERA OF PATIENTS WITH OPHTHALMOPLEGIA AND WITH OTHER SIGNS OF GRAVES' DISEASE

Signs	No. of cases	T.R.C.H. titres							% positive
		Negative			Positive				
		0–20	20–100	Total	100–1000	1000–10,000	Over 10,000	Total	
Recent ophthalmoplegia	6	0	0	0	1	1	4	6	100
Long-standing ophthalmoplegia ..	1	0	1	1	0	0	0	0	0
Other signs of Graves' disease ..	91	37	17	54	20	7	10	37	40·6
Totals	98	37	18	55	21	8	14	43	43·9

by a radioiodine uptake in the clearly thyrotoxic range (Oddie et al. 1960a), or by a clearly hyperthyroid suppression test (Oddie et al. 1960b, Hales et al. 1961).

Of the patients with Graves' disease, only those who were untreated or those who had not received any therapy for at least one year previously were included. Other patients with Graves' disease were excluded to eliminate the possibility of changing antibody titres owing to treatment (Mackay and Perry 1960).

The patients were divided according to their eye signs:

1. *Ophthalmoplegia*, where paralysis of one or more extra-ocular muscles could be demonstrated.

2. *Exophthalmos*, where (*a*) protrusion of the eyes could be shown by an exophthalmometer reading of 23 mm. or more; (*b*) lid retraction, swelling of the lids, or ophthalmoplegia was associated with an exophthalmometer reading of 19 mm. or more (normal average reading 16·9 ± 1·8 mm.); (*c*) there was a clear history of recent bulging of the eyelids with an exophthalmometer reading of more than 21 mm.; or (*d*) the difference between the exophthalmometer readings of the two eyes was greater than 3 mm.

3. *Lid lag*, where no ophthalmoplegia or exophthalmos could be shown by the above investigations but there was definite retraction of the upper lid and at least 2 mm. of sclera was visible above the cornea at rest, or in the upward or downward direction of the gaze (Rundle 1951).

4. *No eye signs*.

Serological Procedure

Antibody titres to thyroglobulin were determined using the tanned-red-cell hæmagglutination (T.R.C.H.) test as modified by Mackay and Perry (1960). Titres of less than 1/100 were considered negative to exclude the possibility of non-specific reactions in this highly sensitive test (Mackay and Perry 1960).

Results

Ophthalmoplegia.—7 patients had ophthalmoplegia. In 6 of these the paralysis was recent; 1 had had paralysis for more than a year. The 6 patients with recent onset all had positive titres. This incidence of positive titres was significantly different from that in the non-exophthalmic group, with a probability of $0{\cdot}01 < P < 0{\cdot}02$. The detailed results are shown in table I.

Exophthalmos.—41 of the 98 patients with Graves' disease had exophthalmos, and of these 66% had positive titres (table II). Using Yates' correction (to exclude falsely significant values in relatively small groups) and applying a χ^2 test, there were significantly more positive titres in exophthalmic patients than in those with no eye signs at all ($0{\cdot}02 > P > 0{\cdot}01$, or, compared with all patients without exophthalmos, $P < 0{\cdot}001$).

Lid lag.—There were 23 patients with lid lag but no exophthalmos. Only 17% of them had positive titres (table II). No relation could be shown by the test used in the exophthalmos group.

TABLE II—T.R.C.H. TITRES OF SERUM OF PATIENTS WITH GRAVES' DISEASE

Signs	No of cases	T.R.C.H. titres							% positive
		Negative			Positive				
		0–20	20–100	Total	100–1000	1000–10,000	Over 10,000	Total	
Exophthalmos	41	10	4	14	13	5	9	27	65·9
Lid lag only	23	10	9	19	2	0	2	4	17·4
No eye signs	34	17	5	22	6	3	3	12	35·3
Totals	98	37	18	55	21	8	14	43	43·9

Discussion

Positive titres were found in 44% of all patients; this figure agrees with that of Mackay and Perry (1960) who found that 47% of thyrotoxic patients had positive titres.

The relation of exophthalmos and ophthalmoplegia with positive T.R.C.H. titres is of considerable interest. Lid lag is associated with hyperthyroidism and usually decreases or disappears when the hyperthyroidism is controlled (*Lancet* 1960), whereas the exophthalmos persists or may even become worse after treatment (Hales and Rundle 1960). The difference in antibody titres in the patients with exophthalmos compared with those with lid lag or with no eye signs may indicate different causal factors in the two groups. Some positive titres in the patients with lid lag or with no eye signs could have been due to the strict criteria to be satisfied before patients were included in the exophthalmic group.

Positive T.R.C.H. titres in patients with exophthalmos may prove useful in studying the factors responsible for the development of this condition.

Summary

Tanned-red-cell hæmagglutinin (T.R.C.H.) titres were estimated in 98 patients with Graves' disease. Of these 41 had exophthalmos (7 also had ophthalmoplegia), 23 had lid lag only, and the remainder had no eye signs.

Positive titres were found to be related to exophthalmos. T.R.C.H. titres may be related to causal factors.

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HIATUS HERNIA

An Anæsthetic Hazard*

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REGURGITATION, with aspiration of stomach contents is a well-known hazard of anæsthesia, particularly for obstetric patients and for those with intestinal obstruction. This subject has been discussed by many authors—among them Balfour and Gray 1933, Irons and Apfelbach 1940, Mendelson 1946, Morton and Wylie 1951, Merrill and Hingson 1951, O'Mullane 1954, Parker 1954 and 1956, Edwards et al. 1956, Lincoln 1957, Scurr 1958, Marshall and Gordon 1958—but none of them has satisfactorily explained why every case at risk does not regurgitate, nor why this phenomenon is sometimes encountered in patients properly prepared for routine non-emergency surgery.

Three years ago I suggested (Dinnick 1957), on theoretical grounds, that the high incidence of hiatus hernia in pregnant women (Mixon and Woloshin 1956, Whiteside 1956) might partly explain why regurgitation is so common during obstetric anæsthesia. I have since seen 4 such cases which support this suggestion.

Typical Case-reports

Case 1.—A nervous primipara with a distended abdomen who suffered severely with heartburn during her pregnancy. She regurgitated during nitrous-oxide/ether anæsthesia for forceps delivery, and later had a severe aspiration pneumonitis of the type described by Mendelson (1946). Five days after delivery a hiatus hernia was shown radiologically.

Case 2.—Another extremely nervous and unusually distended primipara who regurgitated during nitrous-oxide/ether anæsthesia, but had a less severe pneumonia than case 1. She refused to have a barium swallow, but her history was diagnostic. Her heartburn had been severe and she had regurgitated whenever she lay down during the last two months of her pregnancy.

Case 3.—A short, obese, and very nervous woman, who was not delivered at this hospital, was admitted five weeks after delivery to remove an impacted foreign body from her gullet. She had an inhalational pneumonia after œsophagoscopy, and gave a history of a similar complication after ether anæsthesia for a forceps delivery. She had had no previous chest disease. A hiatus hernia was demonstrated radiologically.

Case 4.—This woman received thiopentone only, for surgical induction of labour. She regurgitated and aspirated, but pneumonia did not develop. She was a small woman who subsequently gave birth to a 9 lb. 6 oz. baby, without general anæsthesia. No X-ray was obtained but she had suffered exceptionally from heartburn.

Regurgitation under anæsthesia sometimes takes place—usually during induction—in patients properly prepared for routine non-emergency surgery. Several such cases have been seen, in all of whom subsequent investigation revealed a hiatus hernia.

Case 9 is typical. She was a very nervous fat woman of 51, weighing 196 lb., who was to have a minor operation on her hand. She was adequately premedicated, but after being given some intravenous thiopentone she regurgitated about a cupful of fluid. The resulting pneumonia delayed her discharge from hospital, and she gave a characteristic history of heartburn exacerbated by bending down. A barium swallow in the Trendelenburg position confirmed a hiatus hernia. She had also had pneumonia after another minor operation a few months before.

1 other case gave a similar history, highly suggestive of having regurgitated under a previous anæsthetic; 2 others regurgitated on two separate occasions, and another twice during the same anæsthetic.

Only 2 patients—1 of whom was very difficult to interrogate—failed to give a diagnostic history, but in both of these a hernia was revealed by X-ray examination.

In the remainder—including the 4 obstetric patients—a typical history of heartburn, retrosternal pain, and, in some, frank regurgitation, was easily elicited.

In most of these cases the hernia was not large and a typical X-ray appearance is shown in fig. 1 (case 6).

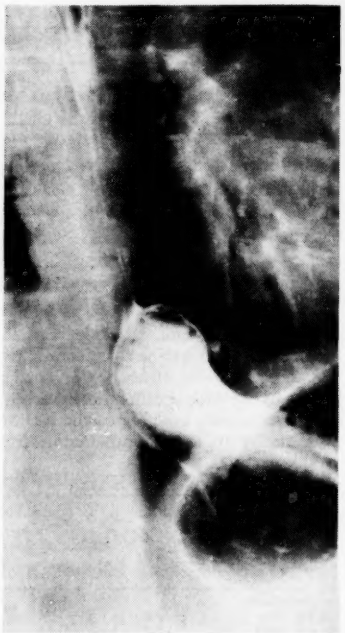

Fig. 1—Typical small hiatus hernia discovered after an episode of unexpected regurgitation under anæsthesia (case 6).

Discussion

These 13 cases were collected in just over a year; and there may have been others which were not brought to my notice, as well as the 2 (not shown in the table) who were neither interrogated by me nor X-rayed. Both were very fat and extremely nervous; 1 regurgitated while being put in the lithotomy position and the other while being turned on his side for sigmoidoscopy.

The only patient investigated who did not have a hiatus hernia was a 196 lb. woman who developed severe laryngeal spasm when accidentally dropped into a steep head-down tilt while being put on the operating-table. This unfortunate incident could well have precipitated some reflux, even though radiological confirmation of a hernia was lacking.

In assessing the incidence of this complication, emergency cases and those with known œsophageal disease were not considered, as these patients can be expected to regurgitate. Similarly, patients with a Ryle's tube in place were also excluded, as were cases of mild

TABLE I—SURGICAL CASES

Case no.	Sex	Operation	Hiatus hernia		Remarks
			Symptoms	X-ray	
3	F	E.N.T.	Yes	Yes	Very nervous; previous incident during obstetric anæsthetic
5	M	Dental	Yes	Yes	
6	F	Mastoid	No	Yes	Regurgitated on two separate occasions
6	M	Gallbladder	Yes	Yes	
8	F	Scar of neck	Yes	Yes	Gallbladder removed without relief
9	F	Mastectomy	No	Yes	Very nervous
10	M	Elbow	Yes	Yes	Regurgitated twice
11	F	Hand	Yes	Yes	Very nervous; previous incident
12	F	E.N.T.	Yes	Yes	
13	F	D. and C.	Yes	No	Very nervous; previous incident gallbladder removed without relief

* Based on a paper read at the 2nd World Congress of Anæsthesiologists, Toronto, on Sept. 7, 1960.

laryngeal spasm in inductions performed by students, and all " incidents " during recovery from anæsthesia.

Unexpected regurgitation, therefore, took place once in about 500 cases.

This is less often than reported by Marshall and Gordon (1958) who had 1 obvious regurgitation in 161 surgical cases, and another in a series of 58 obstetric patients. The general experience that the latter are more liable to this complication is confirmed, for 3 of the cases reported here occurred in a series of only 400 obstetric anæsthetics.

This total incidence of about 2% of clinically significant regurgitations is also compatible with the findings of the many workers (Weiss 1950, Culver et al. 1951, Berson and Adriani 1954, Lincoln 1957) who used previously ingested dyes to detect regurgitation. Although these authors found that between 4%–30% of anæsthetised patients showed evidence of " silent " or unrecognised regurgitation, in very few instances was this clinically significant.

Indeed, Berson and Adriani (1954), whose 926 patients made up by far the largest of these series, stated that in none of their cases was regurgitation detected clinically except when the patient vomited during a difficult induction. In 150 of their cases induction was described as difficult, with an incidence of regurgitation or vomiting of 24%; while in the remainder, where induction was smooth, it was 11%.

This relation between technical anæsthetic difficulties and regurgitation noted by Berson and Adriani (1954) is consistent with the earlier observations of Weiss (1950) and of Culver et al. (1951), that this complication arose more often with inexperienced anæsthetists.

All three authors agreed that regurgitation was more likely with the patient on his side, but their results are conflicting for patients in other positions.

None of these workers, nor any of those mentioned earlier, discuss the build, age, or weight of their subjects.

The common factor, apart from the hiatus hernia, in these patients is that all were obese—some grossly so—and that all except 1 were aged 50 or more (table II). This is higher than the average age of general surgical patients admitted to this hospital. (Middlesex Hospital 1959.)

Fat people are often difficult to anæsthetise. There are many reasons for this: (1) the mechanical embarrassment to effective ventilation; (2) the physical problem of saturating them with sufficient quantities of drugs; (3) coexistent bronchitis; and (4) the short fat neck which makes maintenance of a clear airway difficult.

This is the build, especially if the patient is middle-aged or older, known to be associated with hiatus hernia, and I would therefore suggest that this abnormality and the associated tendency to regurgitation and laryngeal spasm provides a further reason why these people often prove troublesome to the anæsthetist. If this hypothesis is correct then an explanation must be sought why all patients with this abnormality do not regurgitate.

TABLE II—PHYSIQUE OF SURGICAL PATIENTS

Case no.	Sex	Age	Weight (lb.)	Remarks
3	F	43	?	Very short and fat
5	M	60	170	Short and fat
6	F	61	148	Very short and fat
7	M	61	154	
8	F	54	182	Gross
9	F	52	139	Very short and fat
10	M	56	210	Gross and alcoholic
11	F	51	182	Gross
12	F	51	182	Gross
13	F	54	168	Very short and fat

Mechanism of Regurgitation

For regurgitation to take place several conditions must be fulfilled simultaneously:

1. There must be fluid in the stomach. This should not be so in properly prepared cases; nevertheless it is often found, especially if extreme nervousness has delayed gastric emptying. 6 of the patients described here were unusually nervous. Distension of the stomach, though obviously of great importance in cases of intestinal obstruction, is unlikely to have been a factor in the patients reported in this paper.

2. The cardia must become incompetent. The complexities of the normal anatomy or physiology are beyond the scope of this paper (Atkinson et al. 1957, Ingelfinger 1958, Botha 1959) as also are the varieties of hiatus hernia (Allison 1951, Marchand 1957). All that need be said is that many patients with this deformity are known to have a tendency to gastro-œsophageal reflux.

3. There must be a higher pressure in the stomach than in the œsophagus. A raised intra-abdominal pressure is known to produce this (O'Mullane 1954, Marchand 1955, and others). Indeed, to raise this pressure deliberately is an accepted method of demonstrating a hiatus hernia on radiological examination. All the cases in this series probably had a raised intra-abdominal pressure, although in only 5 of them was posture an aggravating factor. A reduction in intrathoracic pressure will also increase the gastroœsophageal pressure-gradient. While some fall occurs in normal inspiration, especially if forceful, it is much greater when there is also an obstruction to inspiration. The importance of this mechanism in producing reflux was emphasised by experiments in man by O'Mullane (1954), and it has been directly observed during œsophagoscopy by him and by Sinclair (1959): that reflux occurs only during inspiration was shown by Creamer (1955).

4. The upper œsophagus and cricopharyngeus must also be relaxed for regurgitation to take place into the pharynx; although these muscles are relaxed by anæsthetic and relaxant drugs, this mechanism is of secondary importance in comparison with that just described for the cardia.

Evidence is against there being any relaxant effect on the cardia by the commonly used anæsthetic drugs (O'Mullane 1954), but this might possibly happen in the rare case where striped muscle extends the full length of the œsophagus That this is sometimes true has been shown by Arey and Tremaine (1933)

Thus, although a hiatus hernia is an important disposing cause of reflux, an increase in the gastroœsophageal pressure-gradient is usually required as well. Although a raised intra-abdominal pressure from obesity, pregnancy, or posture, or a combination of these factors may be sufficient to cause reflux, this is far more likely if the intrathoracic pressure is also lowered by an obstruction to inspiration.

The reduction in intrathoracic pressure can, and does, happen all too easily under anæsthesia, and the extent of the fall in intrathoracic pressure depends on the intensity of the inspiratory efforts which are made in an attempt to overcome the obstruction. I have found that this fall may be to as much as 60 cm. H_2O below atmospheric pressure in anæsthetised patients with active respiratory movements.

I would suggest, therefore, that these two factors—inspiratory obstruction and intensity of respiratory efforts—are of overriding importance in determining whether a patient with a tendency to regurgitate does in fact do so when anæsthetised.

There is further evidence to support this contention:

1. In none of the cases presented here can an episode of respiratory obstruction be excluded. On the contrary, in several of them who had awkward jaws and short necks, it is most likely to have been present. In one patient (case 5) it was deliberately produced, while in another (case 10) it was shown to have precipitated regurgitation on two occasions.

Fig. 2—Diaphragm seen from below at laparotomy performed under light general anæsthesia and bilateral intercostal nerve block. With normal quiet inspiration it is difficult to see the hiatus. (This patient did not have a hiatus hernia.)

2. The findings of those workers already mentioned show that regurgitation is more likely when the anæsthetist is inexperienced or when the induction is difficult. Both these situations mean that inspiratory obstruction probably took place; and, because most of their patients received only gas, oxygen, and ether, without previous thiopentone, that the inspiratory efforts to overcome this obstruction were considerable. This explains why their regurgitation-rate was relatively high, and also partly explains the high rate which is observed in obstetric cases, because these patients usually make very active respiratory efforts, and because they are often given the gas/oxygen/ether sequence.

3. Direct observation has confirmed that the depth and forcefulness of inspiration are indeed important factors. This was shown by a simple experiment. In patients undergoing laparotomy under regional analgesia and light nitrous-oxide anæsthesia, the diaphragmatic hiatus was exposed (fig. 2) (Ranger, unpublished). CO_2 was then administered, and when respiration became deep and forceful, the crura were seen to open on inspiration (fig. 3); and, in 1 case, a previously reduced hiatus hernia was sucked briskly back into the thoracic cavity.

The likelihood of all these factors coinciding is obviously small. This must account for the discrepancy between the 0·2% incidence (0·5% if only patients over 45 are considered) of previously unsuspected hiatus herniæ discovered in the manner described, and the estimated 3–14% of symptomless herniæ in the general population (Desmond 1958).

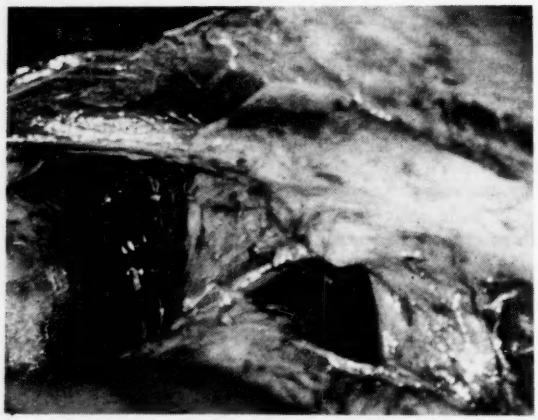

Fig. 3—The same case as in fig. 2 after stimulating respiration with CO_2. The hiatus is seen to be widely open during inspiration.

Although the evidence of the cases described here strongly supports the hypothesis that a hiatus hernia is an important factor disposing to regurgitation under anæsthesia, these cases are not supported by a control series of similar age and build, because it was not considered justifiable either to inflict a barium-swallow examination on every patient, or to obstruct their respiration deliberately in the hope of producing reflux.

Retrospective Inquiry

Because of the absence of controls, the notes of 100 patients in whom a hiatus hernia had been diagnosed were examined. As expected, these patients were elderly and overweight. The average age of the 67 women was 61·3 years; the men, 52. Their weight averaged 147 lb. for the women and 161 lb. for the men, but nearly half of those who weighed less than the average were specifically recorded as obese.

These figures agree with the generally accepted findings in these cases, and so do the associations with gall-bladder disease (12%), other herniæ (9%), and gastric or duodenal ulcers (4% each). 3 cases also had duodenal diverticula.

28 of these patients were operated on for repair of their hiatus herniæ, and these would have had a tube passed into the stomach before operation; moreover, the anæsthetist would have been aware of the possibility of regurgitation, and in fact there was no record of any incident suggestive of such an occurrence.

TABLE III—RETROSPECTIVE INQUIRY

Case no.	Sex	Age	Weight (lb.)	Operation	Remarks
14	M	31 32	168 190	Gallbladder Incisional hernia	Inhalational pneumonia after both anæsthetics. Regurgitation noted on each occasion
15	F	42	129	Hysterectomy	Very short. Inhalational pneumonia
16	F	68	136	Gallbladder	Very short. Inhalational pneumonia
17	M	53	170	Minor rectal	Cough with sputum ever since anæsthetic
18	F	44	168	Simple mastectomy	"Collapsed under the anæsthetic"

Of greater interest in the present context is an analysis of the 30 patients who underwent an operation for reasons other than the repair of hiatus hernia. Of these, 3 were anæsthetised in the reverse Trendelenburg position to obviate the risk of regurgitation. 3 others were thin and wasted and did not have a raised intra-abdominal pressure. This applied also to another man, who although weighing 140 lb., was tall and had recently lost over 42 lb. because of diabetes. 1 other case was considered unlikely to regurgitate—he had a severe stricture of his œsophagus above a small hiatus hernia. All these patients were anæsthetised without incident; as were 3 others, all for cholecystectomy, about whom there was some uncertainty whether their hiatus hernia was present at the time of operation.

Of the remaining 19, all of whom were obese and in whom there was clear evidence of a hernia at the time of operation, no fewer than 5 had major complications of anæsthesia.

In case 18, the evidence is admittedly speculative, but anoxia due to laryngeal spasm after regurgitation of gastric contents is a well-recognised cause of "collapse" under anæsthesia.

The other patients all had clear evidence of pneumonia on the first day after operation, which is highly suggestive of an episode of regurgitation and aspiration. Indeed, in case 14,

regurgitation during the induction of anæsthesia was noted on two separate occasions.

The possible fallacies inherent in a retrospective investigation of this kind are appreciated; nevertheless these cases appear to provide considerable corroborative evidence that a hiatus hernia adds appreciably to the risk of anæsthesia.

It is also worthy of comment that 5 of the 100 cases reviewed underwent cholecystectomy without relief of their symptoms, and this also applies to 2 of the 9 patients in table I.

Practical Implications

If it is agreed that hiatus hernia does carry an increased risk to the patient when anæsthetised, then it behoves the anæsthetist, during his preoperative visit, to seek symptoms suggestive of this condition—retrosternal pain, heartburn, or frank reflux on lying down or bending over.

He should be particularly on the alert if the patient is very obese and over 50, or if she is in late pregnancy.

If a positive history is obtained, then that patient should be regarded as likely to regurgitate under anæsthesia and should therefore be induced by one of the techniques used in cases of intestinal obstruction.

Probably the most suitable, and widely used at present, is that in which the patient is induced and intubated with a cuffed tube in the reverse Trendelenburg position (Morton and Wylie 1951, Snow and Nunn 1959).

Summary and Conclusions

An episode of regurgitation under anæsthesia may be associated with a previously unsuspected hiatus hernia. Inspiratory obstruction may play a part in precipitating such episodes.

Hiatus hernia is an anæsthetic hazard, and a history indicative of this condition should be sought preoperatively, particularly in obese patients over 50 and in women in late pregnancy.

Patients with such a history should be regarded as particularly liable to regurgitate, and should therefore be prepared and anæsthetised in the same way as are those with intestinal obstruction.

I am particularly indebted to Mr. D. H. Patey for the opportunity of observing the diaphragmatic hiatus in patients under his care, and upon whom he and Mr. Ian Ranger operated. I must also express my gratitude to the members of the anæsthetic department who reported many of these cases to me; and to the consultant surgeons, under whose care they were, for permission to investigate them. I must also thank Dr. C. G. Whiteside for most of the radiological investigations, and the staff of the Middlesex Hospital photographic unit for the illustrations.

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Addendum

Since this paper was written, 2 further cases have been seen which emphasise the importance of the preoperative inquiry.

Case 19.—A short fat woman of 48, weighing 140 lb., gave a diagnostic history, although her symptoms had not been sufficiently severe for her to seek medical advice. Induction of anæsthesia with endotracheal intubation in the head-up position was uneventful, but when she was put in the Trendelenburg position for hysterectomy, a cupful of fluid flowed out of her mouth. When the abdomen was open the surgeon confirmed the diagnosis of hiatus hernia.

Case 20.—An obese woman of 54, weighing 158 lb., was presented for a dilation and curettage. She was anæsthetised supine and regurgitated after the thiopentone. The characteristic history of hiatus hernia which she gave later had not been elicited before. An X-ray confirmed the diagnosis, and further inquiry showed that she had had an inhalational pneumonia after a breast operation a year earlier.

SODIUM METHICILLIN IN ROUTINE THERAPY

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THE isolation of the penicillin nucleus, 6-aminopenicillanic acid (Batchelor et al. 1959), has made possible the synthetic production of new penicillins by the addition of different side-chains to the nucleus. One of these new products, the potassium salt of 6-(α-phenoxypropionamido) penicillanic acid—potassium phenethicillin (penicillin B or 'Broxil')—has proved to be well absorbed when given by mouth, but to differ little from penicillin G in activity on penicillinase-producing strains of *Staphylococcus aureus* (Fairbrother and Taylor 1960). This was disappointing because resistant strains of *Staph. aureus* have become a serious problem in hospital practice.

More recently another form of penicillin has been developed—i.e., sodium 6-(2, 6-dimethoxybenzamido) penicillinate monohydrate (BRL 1241 or 'Celbenin'), which has now been given the *B.P.* approved name of sodium methicillin. The striking feature of this new penicillin is its total resistance to penicillinase (Knox 1960, Rolinson et al. 1960, Thompson et al. 1960a). Clinical trials, moreover, indicate that infections caused by penicillinase-producing strains of *Staph. aureus* can be satisfactorily treated with this new penicillin (Douthwaite and Trafford 1960, Stewart et al. 1960). This is a major achievement; but, though it has been suggested that the menace of the resistant staphylococcus has been overcome, several features require further investigation before methicillin can be widely recommended for general use in the treatment of penicillin-resistant staphylococcal infections.

Methicillin has proved to be much less active than penicillin G. For therapeutic purposes it is necessary to give 1 g. intramuscularly every 4–6 hours (Knudsen and Rolinson 1960), which is expensive and inconvenient. In treating experimental infections in mice, it has been shown

that erythromycin was more effective than methicillin (Thompson et al. 1960b). Hence it seemed that the place of methicillin in the treatment of resistant staphylococcal infections had yet to be determined. We therefore decided to investigate (1) the comparative in-vitro activity of penicillin G, methicillin, and erythromycin, particularly against penicillinase-producing strains of *Staph. aureus*, and (2) the possibility of the development of resistance to these antibiotics.

Methods

Sensitivity tests on the different organisms were performed by the serial-dilution technique. Doubling dilutions of the various antibiotics were prepared in special assay broth, and, to 0·5 ml. volumes, 0·02 ml. of an overnight broth-culture was added undiluted. Readings were made after overnight incubation, usually for 18 hours.

For habituation tests, the organisms growing in the concentration of the antibiotic which just failed to inhibit growth after 1–7 days' incubation were used as the inoculum for the next series of sub-cultures; incubation for 5–7 days was usually necessary with methicillin and penicillin G, but not with erythromycin, before growth was observed in the increased concentrations of the antibiotic. This process was continued for at least ten successive subcultures. The minimum inhibitory concentration (M.I.C.) for that particular antibiotic and the other two antibiotics was determined at various stages in the series.

TABLE I—M.I.C. OF THREE ANTIBIOTICS ON 150 STRAINS OF *Staph. aureus*

No. examined	Antibiotics	μg. per ml. of antibiotic										
		0·06 or less	0·12	0·25	0·5	1	2	4	8	16	32	64	>64
Penicillinase negative 20	Penicillin G	20											
	Methicillin							9	11				
	Erythromycin			8	9	2						1	
Penicillinase positive 130	Penicillin G												130
	Methicillin							52	78				
	Erythromycin			49	66	6				1			8

Results

SENSITIVITY TESTS

Of 150 strains of *Staph. aureus* examined, 20 were sensitive to penicillin G, and 130 were resistant to penicillin G—i.e., were penicillinase producers. All strains had been freshly isolated from active infections except 3 which had proved resistant to erythromycin and penicillin, and had been kept in stock. The results are presented in table I.

With the sensitive strains, penicillin G proved by far the most active of the three antibiotics, with a M.I.C. of 0·06 μg. per ml. or less, compared with methicillin at 4–8 μg. per ml.; erythromycin occupied an intermediate position (M.I.C. 0·25–1 μg. per ml.).

Against penicillinase-producing strains, erythromycin proved most active, 121/130 strains giving a M.I.C. of 0·25–1 μg. per ml.; methicillin occupied an intermediate position (M.I.C. 4–8 μg. per ml.). The production of penicillinase greatly influenced the activity of penicillin G, but had no effect on methicillin or erythromycin. Except for the few strains resistant to erythromycin, this agent was appreciably more active, weight for weight, than methicillin.

The M.I.C. of methicillin was found with all strains, sensitive or resistant to penicillin G, to be 4–8 μg. per ml. This is slightly higher than earlier recorded results, and might have been due to using, for the inoculum in the tests, an undiluted culture of freshly isolated strains of *Staph. aureus*.

Effect of the size of the inoculum.—It is widely accepted that any appreciable change in the concentration of the inoculum may greatly influence the M.I.C. of penicillin G with penicillinase-producing staphylococci, but there is little, if any, effect in the case of non-penicillinase producers (Florey et al. 1949). This difference is mainly due to the action of the penicillinase in the inoculum on the penicillin G.

TABLE II—EFFECT OF DILUTION OF THE INOCULUM (*Staph. aureus*) ON THE RESULTS GIVEN BY THE TWO PENICILLINS

Strains of *Staph. aureus*	Penicillin G		Methicillin	
	Inoculum (undiluted) M.I.C.	Inoculum (diluted 1/100) M.I.C.	Inoculum (undiluted) M.I.C.	Inoculum (diluted 1/100) M.I.C.
A	512	32	8	8
B	512	16	8	4
C	512	4	8	8
D	512	4	8	4
E	512	2	8	4
F	0·06	0·06	4	4

The effect of diluting the bacterial inoculum in the case of methicillin was consequently investigated. The results indicated unequivocally that a 1/100 dilution of an overnight broth-culture of a resistant strain had a striking influence on the results for penicillin G, but had little effect on the results for methicillin (table II). This was expected, and it supports the claim that methicillin is unaffected by penicillinase whereas penicillin G, being readily destroyed by this enzyme is greatly influenced by the concentration of the inoculum. This point is of great importance in comparing the results of different investigations where various strengths of bacterial inoculum have been used.

Mode of action of methicillin.—One of the major advantages claimed for methicillin is that it has a bactericidal rather than a bacteriostatic action on all pathogenic staphylococci (Knox 1960, Stewart 1960). In order to compare the activity of methicillin and erythromycin, 0·02 ml. volumes of penicillinase-producing strains of *Staph. aureus* were added to 0·5 and 4 ml. volumes of broth containing two and four times the M.I.C. of methicillin in one series and of erythromycin in the other. At various stages of incubation at 37°C, 0·02 ml. was removed from each culture and after thorough shaking, dropped on to a separate agar plate and then spread evenly over the surface.

With the 0·5 ml. volumes, containing a relatively more concentrated bacterial inoculum, little change was observed in the resulting growths at the end of 6 hours; but after 24 hours' incubation a heavy growth was still obtained from the erythromycin cultures (containing two and four times the M.I.C.) whereas only a scanty growth was given by the cultures containing methicillin (table III).

With the 4 ml. volumes some bactericidal activity was also shown by erythromycin after 24 hours, but the effect was still more striking in the methicillin series. In all instances the bactericidal effect was more pronounced with four times the M.I.C. than with twice the M.I.C.

DEVELOPMENT OF RESISTANCE

There are conflicting opinions about the readiness with which *Staph. aureus* can habituate itself to methicillin in vitro. Rolinson et al. (1960) found that resistance developed only slowly on serial passage, in increasing concentrations of methicillin, of cultures grown in subinhibitory concentrations of the antibiotic. Stewart (1960), in a limited trial, could not demonstrate any increase in resistance. Elek and Fleming (1960), using gradient plates, were also unable to obtain any increased resistance to methicillin after twenty serial passages.

TABLE III—MODE OF ACTION OF METHICILLIN AND ERYTHROMYCIN FOR *Staph. aureus*

Inoculum	Time (hr.)	Erythromycin		Methicillin	
		2 M.I.C.	4 M.I.C.	2 M.I.C.	4 M.I.C.
"Concentrated" (0·5 ml. volume)	0	C	C	C	C
	6	C	C	+++	++
	24	C	+++	++	±
"Dilute" (4 ml. volume)	0	+++	+++	+++	+++
	6	+++	+++	++	++
	24	+++	++	+	±

C = confluent growth.
+++ = confluent growth with areas of isolated colonies.
++ = heavy growth made up entirely of individual colonies.
+ = light growth (approximately 250 colonies).
± = scanty growth (up to 50 colonies).

TABLE IV—HABITUATION OF *Staph. aureus* TO ERYTHROMYCIN, PENICILLIN G, AND METHICILLIN
(10 passages: M.I.C. in μg. per ml.)

Subcultured in	Strain I—M.I.C. with			Strain II—M.I.C. with			Strain III—M.I.C. with		
	Methicillin	Erythromycin	Penicillin G	Methicillin	Erythromycin	Penicillin G	Methicillin	Erythromycin	Penicillin G
—	4	0·25	256	8	0·5	>512	4	0·5	0·06
Methicillin	128	0·25	64	128	0·5	64	32	0·5	4
Erythromycin	8	>64	256	8	>64	>512	8	>64	0·06
Methicillin/erythromycin mixture	16	64	256	32	64	512	N.D.	N.D.	N.D.
Penicillin G	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	32	0·5	32

N.D. = not done.

On the other hand Knox (1960) trained a penicillinase-producing strain of *Staph. aureus* to grow in 18 μg. per ml. of methicillin; this trained strain also became sensitive to penicillin G, having lost the capacity to produce penicillinase. Barber (1960) obtained mutants resistant to 50 and 100 μg. per ml. of methicillin after twenty to thirty passages on ditch plates.

In attempts to habituate sensitive and penicillinase-producing strains of *Staph. aureus* to erythromycin, methicillin, and penicillin G, serial subcultures were prepared in broth, containing increasing concentrations of antibiotics, from growths of subinhibitory concentrations of the previous series of tests. Incubation was often necessary for 7 days in the case of penicillin G and methicillin before any growth was observed in the increased concentration, whereas with erythromycin resistance developed quickly. The increased resistance after ten successive subcultures with 3 representative strains is given in table IV.

Resistance to erythromycin developed rapidly and to a striking degree (>128-fold) after growth in subinhibitory concentrations of the antibiotic. A similar increase was also obtained after incubation in a mixture of erythromycin and methicillin, but there was little increase in resistance to the methicillin. There was no cross-resistance between erythromycin and the penicillins.

In the case of methicillin, an increased resistance of 16-fold and 32-fold developed in the case of penicillinase-producing strains, and 8-fold with the non-penicillinase producing strains of *Staph. aureus* after ten subcultures. Accompanying this increased resistance was a surprising reduction in the M.I.C. of penicillin G in the case of the penicillinase-producing strains, as reported by Knox (1960); with the sensitive strain there was an increased resistance to both methicillin and penicillin G. This suggests that the loss of resistance to penicillin G by the penicillinase-producing strains was due to reduction in the amount and rate of production of penicillinase by these strains after habituation to methicillin in fluid media. But all strains still produced penicillinase, which could be readily demonstrated by adding a little penicillin to the culture. In the case of the sensitive strains a mechanism different from penicillinase production was involved in the development of the increased resistance in vitro, and this was similar with both types of penicillin.

TABLE V—HABITUATION OF *Staph. aureus* (STRAIN C.69) TO METHICILLIN, AND SUBSEQUENT SUBCULTURE

Procedure	M.I.C. (μg. per ml.) with		
	Penicillin G	Erythromycin	Methicillin
On original isolation	512	0·5	8
After 2 subcultures in methicillin	512	0·5	8
" 6 " " "	512	0·25	64
" 8 " " "	64	0·25	128
" 10 " " "	64	0·5	128
After 3 further subcultures without methicillin	64	0·5	64
" 8 " " "	128	0·5	64
" 11 " " "	128	0·5	32
" 20 " " "	128	0·25	32
" 26 " " "	64	0·5	16
" 28 " " "	64	0·5	16
Variant colony isolated at 44°C	0·06	0·5	8

A strain habituated to methicillin was subcultured serially in ordinary broth every 1–3 days on twenty-eight occasions, and sensitivity tests were performed at intervals; a slow but definite decrease in the resistance to methicillin was observed. The reduced resistance to penicillin G tended to persist (table V). Subcultures of the habituated strains were also incubated in broth at 44°C, which has proved a satisfactory way of obtaining sensitive variants from penicillinase-producing strains (Fairbrother 1956). By this technique one colony of a sensitive variant was isolated during sixteen subcultures. This colony had lost the capacity to produce penicillinase, even in the presence of penicillin, and was fully sensitive to penicillin G, having a M.I.C. of 0·06 μg. per ml., while the M.I.C. to methicillin was 8 μg. per ml. It was coagulase-positive and had the same phage-pattern as the original organism. The many other colonies examined throughout this test, however, showed only minor changes and were quite resistant to the penicillins; they gave the same phage pattern as the original culture.

Discussion

Our results agree with those of other workers in that methicillin is active against penicillinase-producing staphylococci, with a striking bactericidal effect. But methicillin has to be given by intramuscular injection, and, because it is rapidly excreted, 1 g. is required every 4–6 hours; a full course is therefore a tedious and costly business. Moreover methicillin has not a particularly high degree of activity, being, weight for weight, about a hundred times less active than penicillin G against sensitive strains, and some eight times less active than erythromycin against most resistant and sensitive strains.

Without doubt the development of sodium methicillin is a significant advance in the production of penicillin, and methicillin may well be the forerunner of more active products; nevertheless, it seems unlikely at present that this new synthetic penicillin will be widely used in routine practice in view of the above disadvantages.

For sensitive strains of *Staph. aureus*, penicillin G remains the outstanding therapeutic agent. For penicillin-resistant strains, drugs such as erythromycin and novobiocin are still likely to be the first line of attack. They are relatively cheap and are taken by mouth. Though staphylococci do tend to develop resistance when these agents are used indiscriminately, this risk can be reduced if they are used carefully. In our hospital erythromycin has been used for 6 years, and resistant strains have never been a serious problem. In a test sample, collected early in 1960, only 9 of 600 strains of *Staph. aureus* (1·5%) proved resistant to erythromycin. Moreover, in adequate amounts, erythromycin possesses some bactericidal activity.

Like all antibiotics, methicillin should not be used indiscriminately because the development of resistant strains is a possibility. But this type of increased resistance is unlikely to prove a serious problem in vivo. Our results indicate that this is produced in the same way as the resistance which can be acquired in vitro to penicillin G, and

is not due to any activity of penicillinase. With penicillin G, this type of resistance has never been shown by strains isolated directly from infective processes. Recently, Jevons (1961) examined 5440 strains of *Staph. aureus* submitted to the Staphylococcal Reference Laboratory, Colindale, and found that strains from three people—two patients and a nurse—showed increased resistance to methicillin. These people were in the same ward of the same hospital, in which methicillin had been used, and the strains belonged to the same phage pattern. Thus it seems that naturally occurring strains exist, but as yet these are the only reported examples.

Methicillin should be particularly valuable in treating severe fulminating infections caused by resistant strains of *Staph. aureus*, and it should be used, with laboratory control, as an alternative to vancomycin, ristocetin, and kanamycin.

Conclusions

Sodium methicillin (' Celbenin ') was found to be active in concentrations of 4–8 μg. per ml. against all strains of *Staphylococcus aureus* examined. But it is about fifty to a hundred times less active than penicillin G against sensitive strains, and about eight times less active than erythromycin against most strains of *Staph. aureus*. It has a striking bactericidal effect.

Staphylococci readily develop resistance in vitro after successive subcultures in increasing concentrations of methicillin.

It is recommended that methicillin should be reserved for severe infections caused by strains of *Staph. aureus* resistant to the usual antibiotics.

We wish to thank Beecham Research Laboratories, Ltd., for the supply of sodium methicillin (' Celbenin ').

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TOXIC REACTIONS TO INTRAMUSCULAR ADMINISTRATION OF IRON DEXTRAN

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RELATIVELY few untoward reactions to the iron-dextran complex ' Imferon ' have been reported. Those most commonly encountered are local tenderness and a greyish-brown discoloration of the skin at the site of the injection (Cappell et al. 1954, Dempster et al. 1954, Hagedorn 1957). More disturbing reactions which have occurred include headache, vomiting, and fever (Karlefors and Nordén 1958), urticaria and angioneurotic œdema (Callender and Smith 1954), arthralgia (Shafer and Marlow 1959), and transient shock-like conditions (Bourne 1955, Koszewski and Walsh 1958).

A severe generalised reaction, with fever and a characteristic painful enlargement of the inguinal lymph-nodes, has been seen in eleven patients in the past 2 years. All the patients, ten of whom were women, had hypochromic anæmia. Nine, including five women in the postpartum period, had received imferon treatment in a hospital. One patient, treated at home, was admitted to hospital because of the severe reaction, and one was referred to the outpatient department. Three of the patients gave a previous history of allergy. In all except one, one or more previous injections of imferon had been well tolerated.

The total amounts of the drug given before the onset of the reactions, and the schedules of administration are summarised in table I.

Clinical Observations

The clinical features and laboratory findings are summarised in table II.

In every case there was abrupt onset of fever, usually remittent, which lasted from 1 to several days. In six patients the temperature exceeded 39°C (102·2°F). Eight patients had tachycardia.

Painful enlargement of the inguinal lymph-nodes was a constant finding. Severe inguinal pain was the main complaint of six patients. In the remaining five, the pain was moderate but was aggravated by palpation. One patient had rebound tenderness. Five patients complained of severe lumbosacral pain which prevented them from lying on their backs and, in one case, from walking. Four patients complained of headache and one of diffuse muscular pains.

The characteristic greyish-brown pigmentation on the buttocks was seen in seven patients. The degree of skin discoloration was unrelated to the severity of the systemic reaction. No other skin or allergic manifestations were noted.

Laboratory Findings

The leucocyte-counts were normal during the acute febrile period in seven of the ten patients. The remaining three had a mild transient leucocytosis of 12,000–13,000 cells per c.mm. In one patient the leucocytes were not counted during the febrile reaction.

Erythrocyte-sedimentation rates (E.S.R.) were performed in nine patients; all E.S.R.s were increased. In three patients in whom the E.S.R. had been determined previously (cases 6–8) it increased considerably shortly after the onset of the fever (table II). E.S.R. was still increased a week after all symptoms had subsided.

Electrophoresis of serum-proteins showed increased α_2 and β fractions in five out of seven cases. In three patients a follow-up examination 2–3 months later (cases 1, 3, and 4) showed a return to normal.

Illustrative Case-records

Case 4.—A 25-year-old woman with postpartum anæmia received her first injection of imferon on April 21, 1960, and subsequent injections on alternate days. On April 27 she complained of severe pain in the left hypochondriac and lumbar region, made worse by inspiration. Her temperature was 38·2°C (100·8°F). The fever was associated with a normal leucocyte count and an E.S.R. of 58 (Westergren) in the 1st hour. A catheter specimen of urine was normal. X-ray of the chest showed no abnormalities. 2 days later, as the pain worsened nephrolithiasis was suspected, but an intravenous pyelogram was normal. The patient was treated with antibiotics, and by May 3 her temperature had subsided. 2 days later, though she was still receiving antibiotics, the temperature rose to 40·5°C (104·9°F) and she was then transferred to our department. Her general condition was good, contrasting with the high fever. There was tenderness over the sacrum, and enlarged painful lymph-nodes were palpable in the right iliac

TABLE I—DOSE AND SCHEDULE OF ADMINISTRATION OF IRON-DEXTRAN BEFORE ONSET OF REACTION

Case	Age (yr.)	Sex	Indication for therapy	Schedule of administration	Amount received (mg.) before reaction	Previous allergy
1	24	F	Postpartum anæmia	200 mg. every other day	1000	Streptomycin
2	24	F	" "	" " " " "	800	Nil
3	20	F	" "	" " " " "	600	"
4	25	F	" "	" " " " "	800	"Allergy" in childhood
5	25	F	" "	200 mg. every 3 days	600	Penicillin, streptomycin, aspirin, phenacetin
6	29	F	Anæmia of pregnancy	200 mg. every other day	600	Nil
7	45	M	Gastrointestinal hæmorrhage	100 mg. every day	300	"
8	32	F	" "	" " " "	200	"
9	30	F	Non-responsiveness to oral therapy	" " " "	400	"
10	53	F	Vaginal bleeding	Unknown	800	"
11	25	F	Intolerance to oral therapy	100 mg.	100	"

fossa. A delayed reaction to imferon was considered as the probable diagnosis. Antibiotic treatment was discontinued. 4 days later the fever subsided and she was free from pain. 2 months after discharge she was in excellent health and the E.S.R. was normal.

Because of the unusually severe reaction in this patient pulmonary embolism, pyelitis, or nephrolithiasis were considered in the differential diagnosis. Subsequent examinations ruled out these conditions. The presence of fever, painful inguinal lymph-nodes, high E.S.R., and normal leucocyte-count suggested an "imferon reaction"—a diagnosis which was confirmed by the subsequent course.

Case 8.—A 32-year-old woman was admitted to our department on Jan. 19, 1959, with melæna. Because of intolerance to iron treatment by mouth, imferon had been prescribed in a daily dose of 100 mg. About 8 hours after the second injection she complained of headache and of pain in the lower abdomen. Her temperature rose to 38°C (100·4°F). Next morning she appeared very ill and had severe pain in the left iliac region. The temperature rose to 39·5°C (103°F) and the pulse-rate to 140. There was considerable tenderness over the left lower abdomen with local guarding. Two of the left inguinal lymph-nodes were enlarged and very tender. Pelvic examination revealed no abnormalities.

Leucocyte-counts during the febrile period were normal. The E.S.R. in the 1st hour rose from 12 to 70, and it remained raised for another week. The symptoms subsided within 2 days of stopping the imferon treatment.

Though an "imferon reaction" was considered in this case, acute salpingitis was also suspected, because of the severity of the abdominal pain, the high temperature, and the rapid pulse-rate. The association of painful lymph-nodes and high fever with a normal leucocyte-count and a high E.S.R. were, however, considered more characteristic of an "imferon reaction" in the light of our previous experience.

Case 10.—A 53-year-old woman was admitted to a hospital with fever and pain of 2 days' duration in the right lumbar and inguinal regions. A month earlier a diagnostic curettage had been performed because of vaginal bleeding. 10 days before admission she had received the first imferon injection, which was followed by three additional injections at 2-day intervals.

On admission her temperature was 39·5°C (103°F) and her pulse-rate 130 per minute. The right inguinal lymph-nodes were enlarged and painful, and there was lymphangitis in the right groin. Tenderness was present in the right lumbar region. Pelvic examination did not reveal any abnormalities. The leucocyte-count was 12,200 per c.mm., and the E.S.R. was 70 mm. in the 1st hour. The patient was treated with penicillin and streptomycin. 3 days later the inguinal pain had subsided, but she then complained of severe pain in the sacral region, which felt hot to the touch and was moderately swollen and very tender. "Cellulitis" was diagnosed. The leucocyte-count did not rise further. Tetracycline treatment was added, and, though tenderness subsided after 2 days, the fever persisted for another 5 despite the antibiotic treatment.

This patient, the first to come to our attention, did not say that she had had imferon injections until a week after admission. An inflammatory process in the pelvis, epidural abscess, and cellulitis were considered in the differential diagnosis, but were not confirmed by the subsequent course. The fever which persisted for 10 days did not seem to be affected by the administration of various antibiotics.

Discussion

All the patients had a febrile reaction and painful swelling of the inguinal lymph-nodes. There was no evidence of abscess formation, and the administration of antibiotics was of no avail. A similar case was reported by Ross (1955) and three additional cases were published by Jacob et al. (1960). Cases of high fever lasting for several days, but apparently without swelling of the inguinal lymph-nodes, have also been reported (Karlefors and Nordén 1958, Schierbeck 1959). Swelling of the

TABLE II—CLINICAL AND LABORATORY FINDINGS IN PATIENTS WITH TOXIC REACTIONS TO IRON-DEXTRAN

Case no.	Symptoms: Fever: Days	Fever: Maximum °F	Fever: Maximum °C	Pulse-rate	Swelling of inguinal lymph-nodes	Skin discoloration	Lumbo-sacral pain	Other complaints	Laboratory data: W.B.C.	E.S.R.	Serum-proteins: Total (g. per 100ml)	Albumin (%)	Globulins (%): α_1	α_2	$\beta_{1,2}$	γ
1	5	102·2	39	120	Severe	+	+	Headache	9300	50	6·9	25·2	3·6	17·4	21·5	32·3
										11*	8·5*	31·1	5·3	11·4	14·5	37·7
2	5	104	40	100	Moderate	−	+		9500	..	..	..	..	..	..	..
3	3	100·4	38	Normal	"	+	−	Painful buttocks	7000	64	6·4	22	11·7	20·7	22	23·6
										24*	6·3*	43·3	7·3	12	17·7	19·7
4	9	104·9	40·5	120	Severe	+	+	Pain in left flank and hypochondrium	9800	58	6·1	30·5	6·5	16·1	19·5	27·4
										10*	6·4*	34·3	9·0	13·5	15·7	27·5
5	5	100·4	38	100	Moderate	+	−	Pain in thighs	5800	43	5·8	31·7	8·7	14·7	17·7	27·8
6	4	101·3	38·5	120	"	+	+	Painful buttocks; could not walk	13,100	95	6·0	21·9	8·6	17·5	21·1	30·8
										(17)†						
7	8	103	39·5	130	Severe	+	−	Headache	12,400	81	6·3	29·7	9·6	19·2	23·4	18·1
										(23)†						
8	2	103	39·5	140	"	−	−	Headache; low abdominal pain	8000	70	..	..	..	..	..	..
										(12)†						
9	2	101	38·3	Normal	"	−	−	Low abdominal pain								
10	10	103	39·5	120	"	−	+		12,200	70	..	..	..	..	..	..
11	1	101·4	38·6	Normal	Moderate	+	−	Headache; diffuse muscular pains	7600	40	7·5	33·7	7·2	14·2	17·4	27·5

* At follow-up examination. † Before febrile reaction. W.B.C. = white blood-cell count (per c.mm.).
E.S.R. = Erythrocyte-sedimentation rate in 1st hour (Westergren).

inguinal lymph-nodes without fever after imferon injections has already been noted by others (Hagedorn 1957, Jenninson and Ellis 1954).

Imferon, being a substance of high molecular weight, is drained by the lymphatics and has been found localised in the lymphatics of rabbits an hour after intramuscular administration (Beresford et al. 1957). In man large quantities of iron have been detected in the inguinal lymph-nodes draining the injection site (Cappell et al. 1954). 56 days after administration of labelled ^{59}Fe-dextran, radioactivity was still present over the inguinal lymph-nodes. These observations explain the frequent involvement of the inguinal lymph-nodes in the "imferon reaction".

A high E.S.R. was constantly present. Although anæmia and postpartum hypoproteinæmia have been contributory factors, cases 6–8 had a considerable increase in the E.S.R. after the febrile reaction. The raised E.S.R. was associated in some cases with an abnormal elevation of the α_2 and β globulin fractions. Similar serum-protein changes may occur in pregnancy, but this pattern was also found in the male patient.

The cause of reactions to imferon is unknown. It usually appears after several well-tolerated injections (Ross 1955, Karlefors and Nordén 1958, Schierbeck 1959), irrespective of the dose or the frequency of administration. It is unknown whether the reaction is caused by the whole iron-dextran complex or by one of its constituents. According to Callender and Smith (1954) the former seems to be more probable because the separate administration of dextran and saccharated iron oxide produced no side-effects in two patients who had had repeated cutaneous reactions from imferon. Similarly, a hexamethonium-dextran complex has produced fever and subcutaneous granulomas (Groen 1960).

In some of the reported cases (Callender and Smith 1954, Bourne 1955) an allergic or immune reaction to the drug or one of its breakdown products was suspected. Skin and complement-fixation tests, however, were negative, and precipitin reactions were inconclusive (Karlefors and Nordén 1958). In one of our patients (case 9) the resumption of treatment after a short interval was uneventful. This and similar observations reported by others (Hagedorn 1957, Karlefors and Nordén 1958) do not support the concept of hypersensitivity.

Attention has been drawn to the carcinogenic effect of large doses of iron-dextan in rodents (Richmond 1959, Haddow and Horning 1960). An editorial in the *British Medical Journal* (1960), warning against the use of imferon, resulted in its temporary withdrawal from general use. A lively debate followed as to the possible carcinogenic effect of this drug in man; some favoured its continued use (Izak 1960, Duthie et al. 1960). Quite apart from the possible carcinogenic effect, however, the serious side-effects in some of our patients have led us to consider iron-dextran unsuitable for routine use.

Summary

The intramuscular administration of iron-dextran ('Imferon') in eleven patients produced a severe reaction consisting of high fever, tachycardia, painful enlargement of the inguinal lymph-nodes, and severe pain in the lumbosacral region. The leucocyte-counts were normal in seven patients and slightly raised in three. A raised erythrocyte-sedimentation rate was a constant finding. The level of the α_2 and β globulins was raised in five out of seven patients.

The seriousness of these reactions is considered another justification for the withdrawal of iron-dextran from routine use.

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A CAUSE OF ERRONEOUS POTASSIUM LEVELS

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HIGH circulating potassium levels are often found in patients who have no symptoms or signs of hyperkalæmia. Consequently, clinicians have grown to distrust serum-potassium estimations, and clinical biochemists have been forced to expand their range of normal values, thus lowering the sensitivity of the test.

During a recent investigation of the amount of potassium lost from human forearm muscle during exercise, it became apparent that gentle forearm contraction can, in some circumstances, lead to a surprisingly high potassium level in effluent blood from that arm. The question immediately arose: could the ritual of forearm exercise so often encouraged during venepuncture affect the local potassium level?

To answer this question two sets of experiments were designed:

Firstly, a group of healthy adults were investigated under laboratory conditions to determine the level to which potassium could rise in effluent blood from exercising forearm muscle, a deliberate attempt being made to accentuate those factors which might lead to an elevation. In addition, an attempt was made to find out whether sampling from a superficial vein might protect against this effect of exercise.

Secondly, the extent to which forearm exercise was used during venepuncture and its effect on potassium estimations was investigated in routine hospital practice.

Methods

Six healthy men lay at complete rest for five minutes. A cuff was then inflated on the upper arm to about 10 mm. Hg below systolic pressure. This cuff was applied to restrict arterial inflow. A needle was inserted into a vein at the elbow (usually the median cubital) that appeared to drain deep structures and therefore to carry mainly muscle blood (Roddie et al. 1956). Blood was collected before, during, and 15–30 seconds after, 10–15 rhythmic contractions of the forearm muscles.

TABLE I—EFFECT OF FOREARM EXERCISE WITH RESTRICTED ARTERIAL INFLOW ON PLASMA-POTASSIUM (mEq. PER LITRE) IN VEINS DRAINING MAINLY FROM MUSCLE (DEEP) (FOR DEEP $t=4{\cdot}06$; $P=0{\cdot}01$) AND SKIN (SUPERFICIAL)

Subject no.	Deep			Superficial		
	Before	During	After	Before	During	After
1	3·8	6·2	4·6	3·9	5·0	5·7
2	4·4	5·4	6·3	4·4	5·1	6·1
3	4·0	6·7	6·0	4·0	4·8	5·3
4	3·7	5·0	5·2	3·9	4·0	4·0
5	4·6	4·9	5·4	4·4	4·4	4·4
6	4·3	4·3	4·5	4·3	4·3	4·5

This routine was repeated after a five-minute rest, but blood was then taken from a vein midway down the forearm which appeared to drain only superficial structures. In only one experiment (subject 3, table I) were the contractions near maximum strength.

All samples were collected in heparinised nylon syringes, immediately transferred to nylon test-tubes, and centrifuged at 2500 r.p.m. for seven minutes. Plasma-potassium was estimated by flame photometry using standard solutions prepared without the addition of sodium. Reproducibility in duplicate samples was within 0·1 mEq. per litre.

Four medical housemen at a local teaching hospital, who had no knowledge of the study, were asked to withdraw, during their routine venous collections, an additional 2 ml. of blood for a special test. Nothing more was said to them, but a record was kept of the vein punctured and the degree of forearm exercise, if any, during the collection. The serum-potassium level of these samples was compared with a control sample, which I took from the opposite arm five minutes later. This control was taken with the usual venous occlusion, but without forearm exercise and from a vein that seemed to drain superficial structures only. All these samples were collected in glass syringes and were allowed to clot in small glass jars. Jars were labelled with different names and despatched for routine determination of the serum-potassium. The technician estimating potassium had no way of distinguishing the control sera from the others.

Results

If the arterial inflow is restricted, forearm exercise in normal subjects can result in a rise of up to 2·7 mEq. per litre in the plasma-potassium level in a vein carrying effluent blood from muscle (table I). Blood taken from a vein that appeared to drain only superficial structures showed similar, but less pronounced, changes in four experiments. In the remaining two, the potassium changes in deep blood were not reflected in the superficial samples (table I). Subject 3, who showed the greatest rise, exercised to near maximum-strength contraction.

Comparison between the serum-potassium in blood taken by housemen and a control taken without exercise from a superficial vein in the opposite arm shows a highly significant difference ($t=3{\cdot}85$; $P<0{\cdot}01$. Table II).

The four housemen all encouraged forearm exercise during venepuncture irrespective of the test. Occasionally this exercise approached maximum-strength contraction, but in most patients the exercise was slight. Patient 5 did nothing more than flick the fingers back and forth several times and yet the potassium was raised 0·5 mEq. per litre above the control.

TABLE II—COMPARISON OF SERUM-POTASSIUM (mEq. PER LITRE) IN BLOOD TAKEN AT ROUTINE INVESTIGATIONS WITH A CONTROL TAKEN WITHOUT FOREARM EXERCISE ($t=3{\cdot}85$; $P<0{\cdot}01$)

Patient no.	Routine sample	Control sample	Difference
1	4·8	4·0	+0·8
2	5·0	4·8	+0·2
3	5·0	4·7	+0·3
4	4·2	4·2	0
5	4·6	4·1	+0·5
6	4·4	4·4	0
7	4·4	4·1	+0·3
8	4·7	4·0	+0·7
9	4·3	4·2	+0·1
10	4·6	4·0	+0·6

Discussion

It is well known that an exercising muscle loses potassium (Fenn 1936, 1940); and Farber et al. (1951) have shown that gentle forearm exercise results in a significant rise in potassium in blood taken from the cephalic vein. The extent to which potassium can rise and the fact that this rise is of clinical significance is not generally recognised.

These results show that a false potassium value can be expected in almost all blood taken for electrolyte estimations during or after even the most gentle forearm exercise. Though no individual rise in the hospital study was as high as in the experimental group, erroneously high levels clearly often occur in routine practice. When veins are difficult to find, near maximum-strength contraction of the forearm is often encouraged and, when this is combined with puncture of the median cubital vein, the potassium level can rise considerably.

The application of a collecting cuff inflated to near systolic pressure accentuates the rise by reducing post-exercise hyperæmia and thereby concentrating the effluent potassium into a smaller volume. That the collecting cuff may be applied too tightly in practice was illustrated when one houseman had difficulty in withdrawing blood until the cuff was removed. The cuff in this instance was a piece of rubber tubing.

Sampling from a vein draining superficial structures does not consistently protect against this rise in potassium. Besides the obvious connections of deep veins with the superficial network in the region of the cubital fossa, there is evidence of vertical venous channels between deep and superficial veins that can carry blood from muscle to skin during exercise (Cooper et al. 1959).

Complete arterial occlusion, or venous congestion alone, in the absence of exercise does not alter the potassium level in blood distal to the cuff over considerable periods (Harpuder and Stein 1943, Farber et al. 1951).

Other sources of error in this estimation include: (1) the passage of potassium from red blood-cells to plasma or serum on standing (Scudder et al. 1939); (2) clotting, which can cause an increase of 0·5 mEq. per litre in serum compared with plasma, owing to the release of potassium from platelets (Pfleiderer et al. 1959); and (3) contamination with foreign potassium and rupture of red blood-cells. Normally when the cells are separated within two hours of collection (Harrison 1957) and care is taken to avoid hæmolysis—which in any case is immediately obvious from the colour of the plasma—errors from these causes are likely to be small, and therefore errors caused by forearm exercise will assume relatively greater importance.

Changes in other electrolytes have not been extensively investigated in the present study. Sodium and chloride would not be expected to be changed since the circulating levels of these ions is comparatively high and would be altered little by exchanges in muscle.

Because magnesium is highly concentrated in muscle, the level of this ion in effluent blood might conceivably be affected by forearm exercise. This was not found to be so

in an experiment in which plasma-magnesium, estimated by the Titan-yellow method (Orange and Rhein 1951), was unchanged at a time when the potassium had risen 0·5 mEq. per litre.

Because Grob et al. (1957) have shown that resting forearm muscles may be either taking up or losing small amounts of potassium at any instant, the only method of obtaining an accurate potassium value seems to be to sample from a superficial vein with normal venous occlusion, but without forearm exercise.

Summary

The combined effect of forearm exercise and restricted arterial inflow can result in plasma-potassium levels above 6 mEq. per litre in effluent blood from that arm.

This procedure has been shown to cause significant errors in routine hospital practice.

During venepuncture for potassium estimations, exercise should be avoided and a superficial vein selected.

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THE TRIETHYL ANALOGUE OF CHOLINE AND NEUROMUSCULAR TRANSMISSION

A Suggestion for its Trial in Neurogenic Spastic States

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RECENT experiments have drawn attention to the possibility of causing neuromuscular block by interfering with the synthesis of the transmitter substance, acetylcholine. A group of compounds known as the hemicholiniums (Schueler 1955) are believed to cause block in this way, the most active member of the group being HC3 (α, α'dimethylaminoethanol-4, 4'-biacetophenone). HC3 inhibits the synthesis of acetylcholine by nervous tissue (MacIntosh et al. 1956, Gardiner 1957). The neuromuscular block produced by HC3 is characteristically slow in onset and dependent on the frequency of stimulation of the nerve, for before any degree of transmission failure becomes evident the acetylcholine which is already stored in the nerve terminals must be used up. For a full account of the evidence leading to the elucidation of the mechanism of action of the hemicholiniums, a recent review by Schueler (1960) should be consulted.

The transmission failure produced by hemicholinium at cholinergic junctions can be reversed by choline (MacIntosh et al. 1956, Reitzel and Long 1959a and b, Wilson and Long 1959, Chang and Rand 1960, Rand and Chang 1960). Furthermore choline will reverse the inhibition of acetylcholine synthesis produced by hemicholinium (MacIntosh et al. 1956, Gardiner 1957). The toxicity of hemicholinium in mice is also antagonised by choline (Schueler 1955, Pfeiffer 1959).

Few other drugs are known which act in a similar way, although Gesler et al. (1959) have shown that the actions of WIN 4981 (3, 6-bis [3-diethylaminopropoxy]pyridazine bismethiodide) resemble those of hemicholinium.

In 1946, Keston and Wortis showed that in mice the toxicity of the triethyl analogue of choline, N-triethylaminoethanol (T.E.C.), was antagonised by choline. This finding, which we have confirmed experimentally, suggested to us that T.E.C. might possess an action similar to that of hemicholinium.

Methods

Experiments were made on conscious rabbits, on the isolated diaphragm/phrenic-nerve preparation (Bülbring 1946), on rabbits under urethane anæsthesia, and on cats under chloralose anæsthesia.

Results

In conscious rabbits the intravenous injection of 5–50 mg. per kg. body-weight of T.E.C. (base) produced, after about 15 minutes, a weakness of voluntary muscle resembling that seen in myasthenia gravis. If left to themselves the rabbits injected with 5–25 mg. per kg. maintained normal posture. When exercised the animals ran normally at first, but the movements soon became weaker, and at this stage the righting reflex was temporarily lost after three or four trials. The righting reflex was regained within a short time, and this procedure could then be repeated.

The rapidly developing weakness after excessive activity could be demonstrated in another way. If a limb was forcibly extended, the rabbit at first responded by rapidly flexing the limb. After two or three repetitions of this stimulus, however, the limb remained in the extended position for a few minutes. The drug effect appeared to have passed off about an hour after injection, although cumulative effects were observed if a second injection was made within 2 hours of the first. With the smaller doses muscular weakness could be produced without impairing respiratory movements. The ratio of the dose which produced definite muscular weakness after exercise to the dose producing death by respiratory failure was approximately 1/10.

In the isolated diaphragm preparation of the rat, the addition of T.E.C. to the bathing fluid in a concentration of 200 μg. per ml. caused a slowly developing decrease in the maximal twitches elicited by rapid stimulation of the nerves.

Similar results were obtained after intravenous injection in anæsthetised rabbits and cats. In these experiments maximal twitches of both tibialis-anterior muscles were recorded simultaneously in response to regularly repeated stimulation of the motor nerves. One muscle was stimulated at a low frequency (6–12 per minute) throughout the experiment, and the contractions of this muscle were not reduced by T.E.C. The other muscle was stimulated at higher frequencies, and the contractions slowly became smaller after the injection of T.E.C. In the cat the minimum frequency necessary to demonstrate the effect was 60 per minute (1 per second). In the rabbit we were unable to affect the response to single shocks at a frequency of 60 per minute, but when short tetanic bursts were applied to the nerve at 5-second intervals (100–250 per second for 0·2 seconds) failure developed. In both species the peak of the effect was reached after 10–30 minutes of continuous stimulation, and the contractions recovered 40–60 minutes after the time of

injection. This recovery shows that the decrease in tension was not a consequence of fatigue. During the paralysis produced by T.E.C. the close arterial injection of acetylcholine caused a contraction of the tibialis-anterior muscle of the cat, which was the same as that recorded before T.E.C. This result shows that the sensitivity of the motor end-plates to acetylcholine, and the contractile power of the muscle itself, were not depressed.

Discussion

These results, with the fact that all of the above effects were reversed by choline, led us to conclude that the transmission failure produced by T.E.C., like the effect of the hemicholiniums, is probably due to an ability of the substance to impair acetylcholine synthesis at the nerve-endings. Although less potent, T.E.C. appeared to possess advantages over hemicholinium in that it was more specific in its action, spontaneous recovery was more complete, and its effects were more readily reversed by choline. Release of the transmitter from cholinergic nerves is known to accelerate the synthesis of acetylcholine, and synthesis must, therefore, be rapid in a hyperactive nerve if full activity of the muscle is to be maintained. Administration of a substance which inhibits synthesis will therefore produce a more selective effect on muscles whose nerves are firing at a high frequency. Our experiments show that after T.E.C. activity is reduced but not abolished. Nerves firing at lower frequencies are less affected by T.E.C., probably because the terminals already contain sufficient preformed transmitter to outlast the time during which T.E.C. remains in the body, and also because the lower rate of synthesis required can probably be maintained in the presence of the drug.

These considerations lead us to suggest that drugs of this type might be of use in the symptomatic treatment of neurogenic spastic states. The rapid rate of nerve firing which is responsible for maintaining the distressing spasticity would itself lead to failure of response. Other muscles, whose nerves are firing at a considerably lower rate, would still be capable of producing muscle activity. Thus it might be expected that T.E.C. would act specifically to deplete the acetylcholine from those nerves which are producing the spasticity.

Summary

The triethyl analogue of choline (T.E.C.) produces muscular weakness in exercised rabbits in doses which do not affect restrained rabbits. T.E.C. produces a neuromuscular blockade in rapidly stimulated muscles of the cat and rabbit in doses which do not affect the responses of a muscle stimulated at a slower rate.

A drug with such actions might be useful in the control of neurogenic spastic states.

We are grateful to Ward, Blenkinsop & Co., Ltd., for a gift of triethylaminoethanol chloride, and to Dr. E. A. Gill of the Department of Pharmacology, Oxford, for a gift of triethylaminoethanol iodide. One of us (M. J. R.) is indebted to the Wellcome Trustees for a fellowship.

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ACTIVITY OF THE TRIETHYL ANALOGUE OF CHOLINE IN SUPPRESSING EXPERIMENTAL TETANUS

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THE ability of the triethyl analogue of choline, N-triethylaminoethanol (T.E.C.), to produce a neuromuscular block by inhibition of acetylcholine synthesis without apparently impairing respiration or abolishing all voluntary movement, has prompted Bowman and Rand (1961) to suggest its use in the treatment of neurogenic spastic states. Tetanus is an obvious disease in which the relief of muscle spasm is of great therapeutic importance. We have therefore studied the effect of T.E.C. on experimental tetanus in rabbits, because the results of such experiments can be related to clinical tetanus.

Method

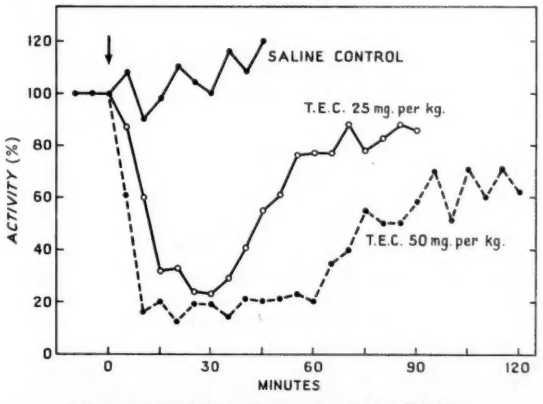
A method of evaluating drugs in experimental tetanus, described by Laurence and Webster (1958a), involves the induction of tetanus in one hind limb of a rabbit by intramuscular injection of the toxin of *Clostridium tetani*. The resulting muscle spasm is measured by quantitative electromyography, and the results are expressed as percentage changes in activity. Drugs can be accurately compared by this method (Laurence and Webster 1958b).

Three rabbits with local tetanus were each given two doses of T.E.C. on consecutive days, and a control record was made from each.

Results

The time-courses of muscle activity after each dose and during a control period are shown in the figure. The onset of effect was delayed for several minutes, not being immediate as with mephenesin or chlorpromazine. A dose/response relation evidently exists, the T.E.C. reducing the tetanus, over $1^1/_2$ hours, by 68% at 50 mg. per kg. body-weight and by 39% for 25 mg. per kg.

Control limb-muscle activity in the uninjected hind limb, which is not shown in the figure and which was about 15% of that of the tetanus-injected limb, was halved by 50 mg. per kg. of T.E.C., and hardly affected by 25 mg. per kg. Respiration and consciousness appeared, on inspection, to be unaffected.



Time-course of the anti-tetanus activity of T.E.C.

Mean results are shown for three rabbits. Tetanus activity (ordinate) is expressed as the mean activity per minute during successive 5-minute periods after injection, compared with the activity before injection. The arrow indicates the time of all injections.

A normal rabbit was given 50 mg. per kg. of T.E.C., and the effect of repeated periods of exercise, described by Bowman and Rand (1961), was confirmed.

Discussion

Clearly T.E.C. can control experimental tetanus temporarily, and it is reasonable to assume that it would have a similar effect in man, as do other drugs which are active against tetanus. If T.E.C. blocks the synthesis of acetylcholine without depleting undischarged stores one would not expect it to prevent an initial convulsion, but it should prevent convulsions or muscle spasm from persisting. Since T.E.C. appears to have a greater blocking effect on rapidly firing motor nerves than on those conducting fewer impulses, one might hope to gain a selective effect in controlling tetanus while sparing respiration and other normal activity, as is possible in rabbits.

The present drug therapy of tetanus is imperfect. Various centrally acting drugs (anæsthetics, mephenesin, chlorpromazine) are used in attempts to achieve this selective effect; but, since they all leave much to be desired, recourse is sometimes necessary to complete paralysis by neuromuscular block with artificial respiration.

The justification for presenting these early results lies in the fact that T.E.C. has a novel mode of action not hitherto used in medicine, and whilst compounds such as this may prove useless, they must clearly be seriously considered for therapeutic trial in diseases such as tetanus, spastic paralysis, and parkinsonism. Investigations are proceeding with this in mind.

The effect of T.E.C. on normal animals, in which it induces a state comparable with myasthenia gravis, is also of interest. We should like to know whether there is a record of a patient with myasthenia gravis contracting tetanus, and if so, of how he responded.

Summary

The triethyl analogue of choline is thought to cause neuromuscular block by inhibiting the synthesis of acetylcholine at motor nerve-endings. It can control the muscle spasm of experimental tetanus whilst sparing respiration and some voluntary movement.

We are grateful to Dr. W. C. Bowman and Dr. M. J. Rand for telling us about N-triethylaminoethanol.

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SURGICAL TREATMENT OF DUODENAL ULCERATION IN TWO HÆMOPHILIACS

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IN hæmophilia hæmatemesis and melæna are common and sometimes are severe, taking place repeatedly at short intervals with considerable danger to life. In most such cases no local lesion can be found, and reliance must be placed on blood-transfusion during acute episodes of bleeding. In the past, even when there was definite evidence of peptic ulceration, few cases were operated on, owing to the risk of uncontrollable bleeding. Now that concentrated preparations of animal antihæmophilic globulin (A.H.G.) are available, hæmophiliacs can be operated on with less risk, and successful operations for various disorders have been reported (Macfarlane et al. 1957, Christie et al. 1960).

In this paper we report the cases of two hæmophiliacs with proven duodenal ulceration who were treated by gastrojejunostomy and selective vagotomy. The first patient had had repeated attacks of severe melæna, endangering life; the second had constant severe epigastric pain, not responding to medical treatment, which had finally prevented him from working.

Materials and Methods

Animal Antihæmophilic-globulin Concentrate

In both patients, the material used (supplied by Crookes Laboratories Ltd.) had been prepared from porcine plasma by the method of Bidwell (1955).

This material is put up as a white powder in ampoules, each containing approximately 200 units of A.H.G. activity (each unit being equivalent to 4 ml. of human plasma) and is dissolved in physiological saline immediately before use.

Each dose was assayed for A.H.G. activity before use, and the values for the plasma equivalents of the doses, shown in figs. 1 and 2, were arrived at by using the average of all the results obtained for each particular batch. This routine was followed as previous experience has shown that A.H.G. activity varies considerably from batch to batch, and storage may lead to deterioration of individual ampoules.

Bovine A.H.G. material (supplied by Messrs. S. Maw, Son & Sons), which was kept in reserve, was not required in either case. Porcine A.H.G. was used in preference to bovine A.H.G. because at the time more of the former was available.

Administration of A.H.G.

The animal A.H.G. was administered intravenously through a small needle (S.W.G.21), which was removed immediately after the completion of each dose. Since concentrated solutions of animal A.H.G. cause pain along the course of the vein, the doses

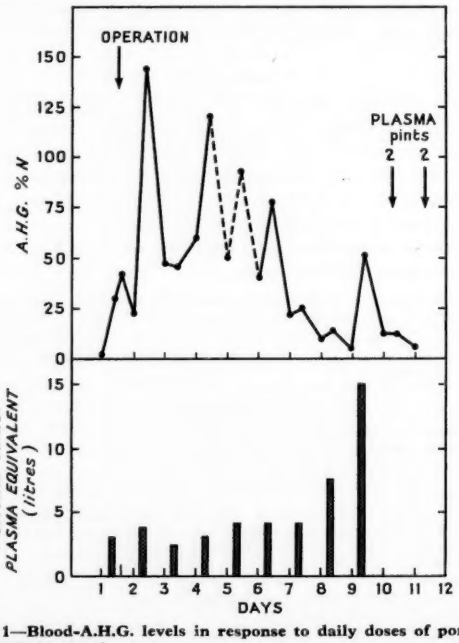

Fig. 1—Blood-A.H.G. levels in response to daily doses of porcine A.H.G. in case 1.

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were diluted with saline solution to a final volume of 200–400 ml., according to the size of the dose. Each dose was given over a period of about 20 minutes.

There was no apparent inflammation of veins, even when the same vein was used for several successive doses.

Pre-treatment samples of blood were obtained through the infusion needle, and post-treatment samples from the opposite arm.

Laboratory Investigations

Lee and White clotting-times (normal range 4–10 minutes), prothrombin-consumption index (normal range 0–15%), and platelet-count (normal range 150,000–300,000 per c.mm.) were all done by the techniques described by Biggs and Macfarlane (1957). A.H.G. (normal range 50–200%) was assayed by the method of Biggs (1957).

Case-reports

Case 1.—This 54-year-old man has a lifelong history of excessive bleeding. He bruises easily, has frequent epistaxes, and bleeds excessively after extraction of teeth. He has had no joint involvement, however, and can lead a normally active life.

In the 25 years before this admission [R.I. no. 254073], he had many episodes of melæna, and had required several transfusions. Between August, 1958, and May, 1959, he was admitted to the Radcliffe Infirmary four times with severe melæna and hæmoglobin levels of between 37% and 57%. On each occasion transfusion of between 5 and 10 pints of fresh whole blood was needed to control bleeding. Several other smaller bleeding incidents were treated at home, and he was unable to work during this period.

Three of his brothers were also hæmophiliacs, one having died of bleeding following an operation on his lip. Two cousins on his mother's side are also " bleeders ", and a further distant cousin has proven Christmas disease (fig. 3). One surviving brother (a twin to the patient) had a laparotomy elsewhere for hæmatemesis and melæna, but no ulcer was found. He had a large wound hæmatoma; he required several pints of blood, and eventually stopped bleeding 3 weeks after operation. The other brother recently had a severe acute melæna, and emergency operation was contemplated. Bleeding was eventually controlled by transfusion of 19 pints of fresh and stored whole blood and 2 pints of fresh plasma. Barium-meal examination later confirmed a duodenal ulcer. This was his first episode of gastrointestinal bleeding and there has been no recurrence.

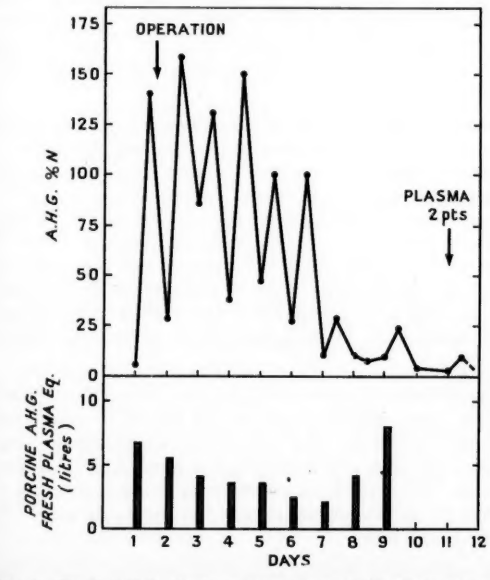

Fig. 2—Blood-A.H.G. levels in response to daily doses of porcine A.H.G. in case 2.

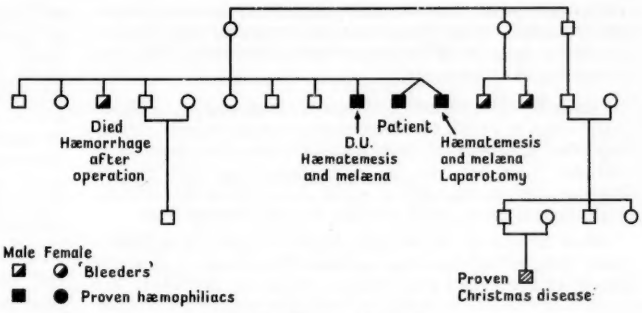

Fig. 3—Family tree of case 1.

The patient was admitted for operation on June 1, 1959, at which time he was not bleeding. General physical examination revealed no relevant abnormalities, and his joints appeared to be normal.

Investigations

The hæmoglobin was 78%, and the platelets numbered 215,000 per c.mm. The clotting-time ($8^1/_2$ minutes), prothrombin-consumption index (13%), and one-stage prothrombin-time (Quick) were all within normal limits, but the blood-level of A.H.G. was only 3%. These findings were consistent with mild hæmophilia.

Two barium-meal examinations (February and April, 1959) showed deformity of the duodenal cap, but neither time was an actual ulcer crater demonstrated.

On June 3, 1959, the patient was given an initial dose of porcine A.H.G., with a consequent rise of blood-A.H.G. level to 30%. 2 hours later a second dose was given, which raised the A.H.G. level to 42%; and, after this second dose, operation was begun.

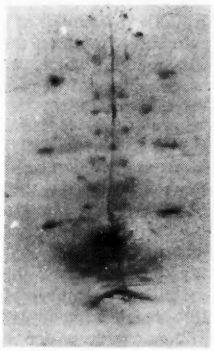

Fig. 4—Small hæmatoma at lower end of wound in case 1.

Operation (Mr. Elliot Smith)

There was a large ulcer on the anterior surface of the first part of the duodenum. No other abnormality was noted. Selective vagotomy and retrocolic posterior vertical gastrojejunostomy were performed. There was very little bleeding during the operation, and the abdomen was closed without drainage using deep tension sutures.

Postoperative Course

Daily doses of porcine A.H.G. were given for 8 days after operation, the size of each dose being determined by the rise in blood-A.H.G. level resulting from the preceding dose (fig. 1). There were no adverse reactions to the A.H.G. until the final dose, which was followed by a rigor and backache, believed to be anaphylactic in origin. The administration of porcine A.H.G. was discontinued because of this reaction. The clips in the skin edges were removed on the 7th day after operation, at which stage the wound was healthy. There was no hæmatoma, and the dressings were only slightly bloodstained. The skin sutures were removed on the 8th day, and deep tension sutures on the 10th day, after operation. On the 9th day there was a little oozing from the lower end of the wound, which was controlled by daily infusions of fresh plasma for 2 days (fig. 4). There was no clinical evidence of gastrointestinal bleeding, but as the hæmoglobin had fallen to 63% on the 10th day, the patient was given 2 pints of stored whole blood. He was

discharged home 3 weeks after operation with the wound firmly healed. Since operation he has remained well, has had no further episodes of melæna to date (September, 1960), and is working as a messenger.

Case 2.—This patient, a 33-year-old man, received a blood-transfusion as a child for bleeding from a scalp wound. Bleeding after extraction of teeth has required up to 6 weeks in hospital. He has had no hæmarthroses or large bruises, however, and he can lead an active life. His brother and ten male cousins on his mother's side are also hæmophiliacs.

Since he was 10 he has had attacks of recurrent epigastric pain, and several years ago radiography showed a duodenal ulcer. In the 5 years before admission [R.I. no. 282079] he had several episodes of melæna, but did not require transfusion. For a few months before admission the attacks of epigastric pain were so severe and frequent that he was unable to work.

No relevant abnormal physical signs were detected when he was examined, and his joints appeared to be normal.

Investigations

The hæmoglobin was 100%; the platelets numbered 350,000 per c.mm.; the bleeding-time (Ivy) was $2^1/_2$ minutes, and the tourniquet test was negative. The clotting-time was $6^1/_2$ minutes, prothrombin-consumption index 30%, and the A.H.G. level 6%. These results were compatible with mild hæmophilia.

A large ulcer crater in the first part of the duodenum was shown by barium-meal examination.

On Nov. 21, 1959, after a preliminary infusion of porcine A.H.G., which raised the blood-A.H.G. to 140%, operation was begun.

Operation (Mr. Elliot Smith)

This was similar to that performed on case 1. A large active ulcer was found on the anterior surface of the first part of the duodenum, which was considerably deformed. Selective vagotomy and retrocolic posterior gastrojejunostomy were carried out.

Postoperative Course

After operation eight daily doses of porcine A.H.G. were given, and on the 8th day the clips were removed from the skin edge. As the response to the final two doses of porcine A.H.G. was much diminished, the administration of this material was discontinued (fig. 2). No therapy was given on the 9th day, but on the 10th day 2 pints of fresh frozen plasma was infused before the removal of the remaining sutures. Healing had proceeded normally without the formation of a hæmatoma. There was no evidence of gastrointestinal bleeding at any time, and the patient was discharged 3 weeks after operation.

He has remained well to date (September, 1960), and has had no further abdominal pain or melæna.

Discussion

The surgical treatment of peptic ulceration in the hæmophilic patient has until recently proved hazardous and published reports have been few.

Wosnessensky (1930) reported the death of a hæmophiliac after gastrectomy. Emile-Weil (1931) reported a gastro-enterostomy for repeated hæmorrhage from a duodenal ulcer in a patient with hæmophilia. A preoperative transfusion of 300 ml. of whole blood was given. There was some bleeding on the 2nd day after operation, but details of postoperative treatment are not recorded. The patient recovered. A year later, after a fall, he had another hæmatemesis, but no ulcer was shown radiologically.

More recently, Walker (1955) and Desmond (1955) each reported a case of hæmophilia in which gastrectomy was performed for bleeding from a duocenal ulcer and a gastric ulcer respectively. In both patients there was severe post-operative bleeding, only partly controlled by large quantities of fresh blood and plasma in the first case, and of fresh blood only in the second. Prof. A. K. Lowden, of Newcastle, carried out a partial gastrectomy on a hæmophiliac who had repeated severe melæna from a chronic duodenal ulcer (Boon 1960). Fresh plasma was used to control bleeding, and a total of 20 pints of fresh whole blood was given after operation. There are undoubtedly other similar but unreported cases; and obviously not all such cases of peptic ulceration treated surgically end fatally, even in the absence of concentrated A.H.G. materials. In most cases postoperative bleeding has been severe and dangerous, requiring much whole blood despite energetic treatment with plasma.

Since neither of our patients was bleeding at the time, the operation and postoperative treatment could be planned. Partial gastrectomy, with removal of the ulcer, may be preferable for the emergency treatment of acute and continuing hæmorrhage. In these patients gastro-jejunostomy with vagotomy sparing the hepatic and cœliac divisions of the vagus seemed to be the operative treatment of choice, since this procedure carries less risk and a lower morbidity than partial gastrectomy.

During the operation, and for at least part of each subsequent day until the wound was healed, it was planned to keep the blood-A.H.G. level above the arbitrary figure of 30% suggested by Macfarlane et al. (1957). To do this, animal A.H.G. was used rather than human A.H.G., fresh blood, or fresh plasma, since previous experience had shown that these substances were less sure in their action in raising the blood-A.H.G. level. In both patients initial response was good, but porcine A.H.G. had to be discontinued after the 9th day of treatment. At this time the first patient had a rigor accompanied by backache, thought to be of anaphylactic origin; and, in the second patient, even a greatly increased dosage failed to produce a satisfactory rise in the A.H.G. level.

The slight oozing from the wound in the first patient after the cessation of porcine A.H.G. infusions was easily controlled by the plasma infusions given on the next 2 days. Similarly, the second patient was given a fresh frozen plasma infusion to cover removal of the deep tension sutures.

After the removal of the sutures both patients were confined to bed for a further week, as we feel that premature activity following the cessation of A.H.G. therapy may lead to hæmatoma formation in an incompletely healed wound.

The relative shortness of the period for which animal A.H.G. can be used is a considerable disadvantage, and it is obviously desirable to obtain healing by first intention within this period if possible. Macfarlane et al. (1957) found that, by using only one type of animal A.H.G., effective blood-A.H.G. levels could be obtained for 6–10 days only. Further use of this material was precluded by either an anaphylactic type of reaction, as in the first patient, or a lack of response to the material even in very large doses—e.g., 20 ampoules—as in the second patient (fig. 2).

Further cover may be obtained by using another type of animal A.H.G. material, such as the bovine A.H.G., which was held in reserve. The response is not usually so long-lasting, however, and further use is precluded for similar reasons. The total duration of cover using both types of animal A.H.G. varies from patient to patient, but is usually about 12–14 days.

If satisfactory healing cannot be obtained within this time, further cover can only be given by infusions of

other A.H.G.-containing material such as fresh blood, plasma, or human A.H.G. concentrate (Kekwick and Wolf 1957).

These materials, less certain in their response, are adequate for the control of minor oozing, but not for further major surgical procedures.

Summary

Animal antihæmophilic globulin (A.H.G.) was successfully used to control bleeding in two hæmophilic patients who underwent gastrojejunostomy and selective vagotomy for duodenal ulceration.

An arbitrary blood-A.H.G. level of 30% was aimed at during operation. The action of animal A.H.G. in raising the blood-A.H.G. level was found more certain than that of human A.H.G., fresh blood, or blood plasma.

In both patients porcine A.H.G. had to be discontinued after the 9th day. One patient showed an anaphylactic reaction; the other ceased to respond satisfactorily even to large doses of A.H.G. The period of treatment may be prolonged to about 12–14 days by using A.H.G. from a different type of animal. After this, further cover can be given only by using fresh blood, plasma, or human A.H.G. concentrate.

We wish to thank Dr. P. C. Mallam and Mr. A. Elliot Smith for permission to publish details of these patients, and Dr. R. G. Macfarlane and Dr. Rosemary Biggs for their advice and permission to publish the hæmatological findings. We should also like to thank Mr. E. L. Tugwell for the photograph (fig. 4).

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Addendum

Since this paper was submitted for publication a further patient has been treated for a duodenal ulcer by gastrojejunostomy and selective vagotomy. The operation and postoperative period was covered by infusions of animal A.H.G. as in the two cases already described, but the bovine instead of the porcine material was used. The wound was healed 12 days after operation, no postoperative blood-transfusion was required, and the hæmoglobin was 88% (13·0 g. per 100 ml.) on the 14th postoperative day.

Preliminary Communications

ENVIRONMENTAL TEMPERATURE AND URINARY EXCRETION OF 3-METHOXY-4-HYDROXYMANDELIC ACID IN THE NEWBORN

Moore and Underwood [1] recently showed that noradrenaline is thermogenic in several species of newborn mammals. They suggested that it may play a role in normal thermoregulation in the newborn, providing a stimulus to heat production in response to a drop in environmental temperature. We therefore decided to try to determine whether such a mechanism is also important in the control of body temperature in the newborn baby. A direct trial of the effect of noradrenaline was impracticable for a number of reasons; we therefore obtained indirect evidence by measuring the response to a change in environmental temperature of urinary excretion of a major metabolite of noradrenaline and adrenaline, 3-methoxy-4-hydroxymandelic acid (V.M.A.). This was chosen because it can be estimated accurately, and because a much greater proportion of the total pressor amine appears in the urine in this form than in the form of free amine.[2]

METHODS

Sixteen normal full-term male babies, aged between 4 and 9 days, were placed in thermostatically controlled incubators. Each baby spent 24 hours in one incubator, kept as near to 85°F (29·4°C) as possible, followed immediately by a further 24 hours in a second incubator, set at 75°F (23·9°C), or vice versa. The order was determined by random selection, nine babies spending the first 24-hour period at 85°F, and seven at 75°F. All urine excreted during each 24-hour period was collected by Paul's tubing taped about the penis, and pooled. If there was any loss or suspected loss of urine, the experiment was rejected.

Incubator temperatures, measured by a mercury thermometer lying alongside the baby, were recorded at intervals of 1–4 hours. There was considerable fluctuation, mainly related to the periodic removal of babies from the incubator for feeding and bathing. Rectal temperatures were taken at similar intervals by clinical thermometer.

Each baby was out of the incubator for a total estimated time of about 3 hours in each 24 this being the minimum period required for feeding and toilet procedures. Ten infants were breast-fed, and six were bottle-fed with half-cream cow's milk.

V.M.A. was assayed by a modification (to be published) of the method of Sandler and Ruthven.[3 4]

1. Moore, R. E., Underwood, M. C. *Lancet*, 1960, i, 1277.
2. Axelrod, J. *Physiol. Rev.* 1959, **39**, 751.

TABLE I—URINARY EXCRETION OF V.M.A. AND URINE VOLUMES, AT THE TWO INCUBATOR TEMPERATURES

—	Temperature (°F)	Mean	S.D. of mean	Range
V.M.A. output (mg. per 24 hr.)	85	0·344	0·052	0·06–0·71
	75	0·431	0·059	0·13–0·81
Volume (ml. per 24 hr.) ..	85	192·0	26·4	40–393
	75	247·0	33·5	62–487
V.M.A. concentration (mg. per litre)	85	1·98	0·252	0·86–4·00
	75	1·95	0·192	1·02–3·70

RESULTS

There was a significant ($P < 0·01$) increase of 25% in V.M.A. excretion, and also a significantly ($P < 0·001$) increased urine-volume at the lower temperature (tables I and II).

The mean increase in V.M.A. excretion at 75°F in the six bottle-fed babies was 0·06 mg. per 24 hr. compared with 0·01 mg. per 24 hr. in the ten breast-fed babies. In the nine babies who spent the first 24 hours at 85°F the mean increase in V.M.A. excretion at 75°F was 0·07 mg. per 24 hr. compared with 0·11 mg. per 24 hr. in the seven babies who spent the first 24

3. Sandler, M., Ruthven, C. R. J. *Lancet*, 1959, ii, 114.
4. Sandler, M., Ruthven, C. R. J. *ibid.* p. 1034.

TABLE II—ANALYSIS OF THE DIFFERENCES IN EACH OF THE SIXTEEN PAIRS OF OBSERVATIONS

—	Mean of differences *	S.D. of mean	Significance (P)
V.M.A. output (mg. per 24 hr.)	0·087 (+25%)	0·025	<0·01
Urine-volume (ml. per 24 hr.)	53·9 (+28%)	6·1	<0·001
Urine-V.M.A. concentration (mg. per litre)	−0·04 (−2%)	0·14	>0·1

* Value at 75°F—value at 85°F for each baby.

TABLE III—MAXIMUM AND MINIMUM RECTAL TEMPERATURES

Rectal temperature (°F)	Incubator at 75°F		Incubator at 85°F	
	Mean	Range	Mean	Range
Maximum	98·6	97·4–99·1	98·7	98·0–99·8
Minimum	97·4	96·3–98·2	97·7	96·7–98·7

hours at the lower temperature. Rectal temperatures of the babies were slightly higher at an incubator temperature of 85°F than at 75°F, but the differences were not substantial (table III).

At the lower temperature, we noted an increase in the restlessness of the babies.

DISCUSSION

The increase in V.M.A. output at 75°F was somewhat less in bottle-fed than in breast-fed babies. It was also less in those who spent the first 24-hour period at 85°F than in those who were first at 75°F. But we do not think that these differences are meaningful, and we have no comment to make upon them at this stage.

The babies' rectal temperatures were slightly lower at 75°F than at 85°F, but the difference was not enough to warrant detailed analysis. The general similarity supports the view that the babies were in thermal equilibrium at both environmental temperatures. Apart from constitution of food and order of entering the two incubators, environmental temperature difference was the only known variable, and this was presumably sufficient to cause a greater output of V.M.A. in the cooler (75°F) than in the warmer (85°F) condition (table I). Because V.M.A. is derived from both noradrenaline and adrenaline it is not possible to define the source of the extra 25% from these experiments, nor do we know whether this figure represents the full manifestation of additional catecholamine metabolism in the cooler environment.

Quantitative data are available for a number of the pathways by which noradrenaline and adrenaline are degraded in the normal adult.[5] Some evidence also indicates that V.M.A. excretion in the adult male is directly proportional to catecholamine output.[6] But whether the newborn infant excretes metabolites in the same proportion as the adult is not known; little information is available about the enzyme systems concerned in inactivation during the neonatal period. Nor do we know in general to what extent the site of catecholamine action determines the pathway of degradation. A further gap in our knowledge concerns the manner of V.M.A. excretion. Many excretion mechanisms are relatively undeveloped in early life.[7] The possibility therefore exists that increased V.M.A. output in the cold is a function of greater urinary volume (table I).

Despite these uncertainties, a number of possible reasons might explain catecholamine turnover at the lower temperature. There might be greater sympathetic activity in the cardiovascular system; tissue noradrenaline or adrenaline liberation might be increased in association with the restlessness which was observed. An equally valid explanation of the significant increase in V.M.A. excretion which would support the thesis of Moore and Underwood [1] is that it is due directly to an increased liberation of noradrenaline in response to a cold stimulus.

SUMMARY

In sixteen babies aged 4–9 days, there was a significant mean increase of 25% in urinary output of 3-methoxy-4-hydroxymandelic-acid at an environmental temperature of 75°F compared with one of 85°F.

This extra 3-methoxy-4-hydroxymandelic acid might be related to an increased secretion of noradrenaline in response to a cold stimulus.

We are grateful to the mothers who consented to their babies being studied; to Prof. J. H. M. Pinkerton, Dr. A. W. Franklin, and Dr. A. P. Norman for access to their patients and for helpful discussions; and to Sister J. K. Lewis, Sister M. M. Langridge, Miss R. A. Mulligan, and Miss M. B. Duggan for assistance in the collection of specimens.

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5. Kopin, I. J. *Science*, 1960, **131**, 1372.
6. Goodall, McC., Berman, M. L. *J. clin. Invest.* 1960, **39**, 1533.
7. McCance, R. A. *Arch. Dis. Childh.* 1959, **34**, 361.

EFFECT OF A DETERGENT ON GASTROINTESTINAL ABSORPTION OF A STEROID

VERY little is known about the gastrointestinal absorption of steroids, and, as they are expensive, we decided to study this process. Because of the large doses used clinically, and the ease of quantitative analysis by spectrofluorometry, we chose the spirolactone, spironolactone (' Aldactone ').[1]

Fig. 1 shows the plasma levels of spirolactone in four normal subjects after the administration by mouth of 400 mg. of spironolactone alone and with 40 mg. of polysorbate 80 (' Tween ' 80), and also after 200 mg. of spironolactone with 200 mg. of polysorbate. The areas under the curves are much greater when the detergent was given, suggesting greater absorption from the gastrointestinal tract.

Most 3-keto-Δ-4 steroids are reduced by the liver to their relatively inactive tetrahydro derivatives, and the

1. Gochman, N., Gantt, C. L. *J. Pharmacol.* (in the press).

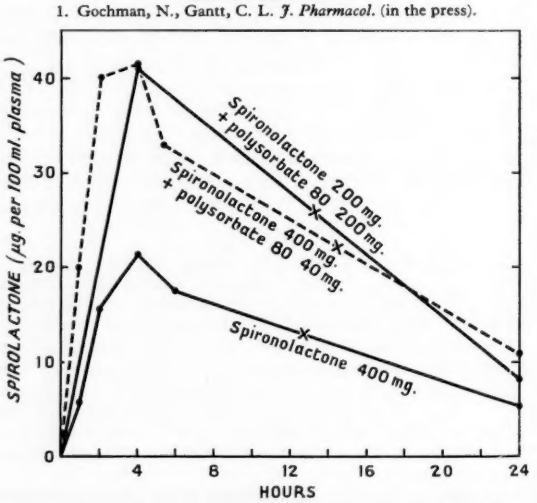

Fig. 1—Plasma levels of unreduced spirolactone after administration by mouth of spironolactone with and without polysorbate 80. Each point represents the average of four normal subjects. x=calculated plasma half-life.

method of analysis of spirolactone used depends on the presence of the 3-keto-Δ-4, 6 configuration.[1] Therefore, the increase in blood-levels of the free compound could be due to its absorption into the lymphatic system without an increase in total absorption from the gastrointestinal tract. Preliminary studies of the concentration of spirolactone in the thoracic-duct lymph of dogs suggest that this is not true. The ratio of the concentration of the steroid in the lymph to that in the peripheral blood did not exceed unity when the steroid was given with and without the detergent.

Another possibility is that the detergent interferes with the metabolism or excretion of the steroid. The " half-life " of spironolactone in the plasma (about 13 hours) is not significantly altered when the polysorbate is given (fig. 1), suggesting that the metabolism is not changed. The recovery of spirolactone from the urine has been consistently greater when the detergent is given than when spironolactone is given alone. The effect of spironolactone on sodium excretion also seems to be enhanced when the detergent is given (fig. 2). Jones et al.[2] presented data

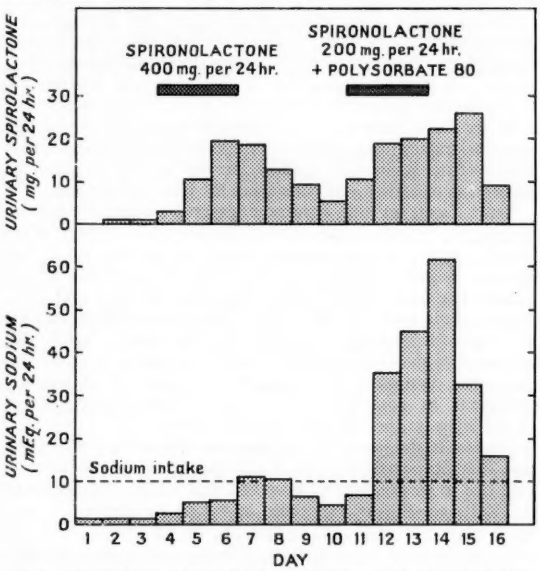

Fig. 2—Urinary excretion of sodium and free unreduced spirolactone in a patient with cirrhosis and ascites given spironolactone alone and with polysorbate 80.

suggesting that polysorbate 80 will promote the absorption of fats and fat-soluble substances from the gastrointestinal tract.

Other steroids are being studied to determine the spectrum of this effect and the possible differences in venous and lymphatic absorption.

Polysorbate 80 is not toxic, being used in foodstuffs,[2] and it is inexpensive. If our findings are applicable to other steroids and fat-soluble drugs, the practical application will be important.

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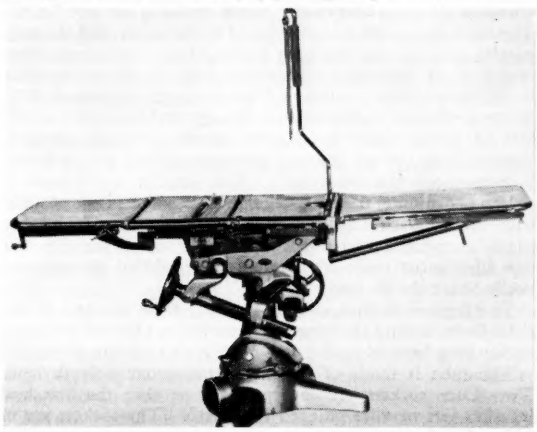
2. Jones, C. H., Culver, P. J., Drummey, G. D., Ryan, A. E. *Ann. intern. Med.* 1948, **29**, 1.

New Inventions

IMPROVED GYNÆCOLOGICAL OPERATING-TABLE

UNNECESSARY physical effort in hospitals must be kept to a minimum in these days of staff shortage; and the lifting of patients to and from the lithotomy position can be avoided by better-designed operating-tables. In the standard table if the Trendelenburg position is maintained in the old-fashioned and dangerous way, with bent legs, the break at the lower end is opposite the patient's knees. With the lower flap lengthened to 28 in., and made detachable, by placing the patient on the table



with her hips opposite the break, the legs can be placed in the lithotomy position with very little or no lifting. Such tables, used for some time at the North Ormesby and Middlesbrough maternity hospitals, have been found to save both time and effort. Otherwise the tables have the standard fittings. A centrally placed recess at the end of the central part of the table allows a vaginal speculum to swing freely. Shoulder-rests can be fixed in the middle of the table if it is desired to tilt the patient slightly with the pelvis raised. Standard lithotomy supports are used, but modifications are being tried. The usual way of maintaining the lithotomy position is unsatisfactory; and probably this is responsible for some of the backache and other troubles after gynæcological operations. Ideally the patient should be easily placed in position by a single-handed person, there should be no undue pressure on the soles of the feet, calves, popliteal spaces, or the neck of the fibulæ, and the surgeon and his assistants should have good access to the operating site.

This table has been made by Messrs. Chas. F. Thackray, Ltd., of Park Street, Leeds.

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TWO-CHANNEL TUBE FOR CAVAL INFUSION

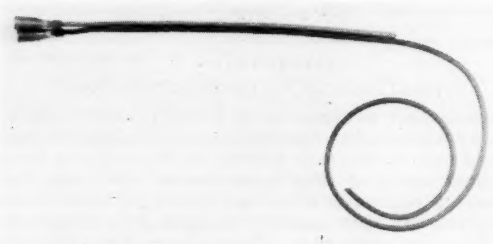
A HAZARD in the treatment of anuria by the intracaval infusion of 50% dextrose solution is thrombosis in the segment of vein occupied by the plastic tube—e.g., the right iliac veins when the tube has been passed into the inferior vena cava from the exposed right long saphenous vein. Attempts have been made to minimise this effect by:

(1) General anticoagulation with heparin, 15,000 units per 24 hours.[1] This adds further risks in a patient already seriously ill.

(2) Addition of heparin to the infused 50% dextrose solution in strengths of either 1000 units per litre,[2] or 2000 units per litre.[3] The heparin, however, is then delivered into the vena cava, and the current of blood draws it away from the area of vein at risk.

The proposed modification employs a specially designed catheter consisting of a twin-channel plastic tube, one of

1. Russell, C. S., Dewhurst, C. J., Brace, J. C. *Lancet*, 1954, i, 902.
2. Ross, J. K. *Post Grad. med. J.* 1957, **33**, 623.
3. Chambers, J. W., Smith, G. *Brit. J. Surg.* 1957, **45**, 160.



Two-channel tube for caval infusion.

whose limbs is a third of the length of the other (see figure). The long saphenous vein is exposed in the groin, and the tube passed up it so that the long limb ends in the inferior vena cava and the short limb ends about 2 cm. inside the opening in the long saphenous vein. The requisite amount of 50% dextrose solution is then infused through the long limb (usually 800 ml. per 24 hours in complete anuria). Heparin solution, 5000 units in 100 ml. isotonic dextrose solution per 24 hours, is infused via the short limb. This implies a drip-rate of 1 drop per minute, the exact regulation of which is not possible with the standard adjusting clips on infusion sets. The rate should therefore be set roughly by adjustment of the clip, and fine adjustment made by varying the height of the infusion bottle above the patient.

The heparin is thus carried centrally from the end of the short limb, around the long limb, perfusing the vein occupied by the long limb—i.e., the area most at risk to thrombosis.

The tube is made of twin 6 French-gauge polyethylene. Two Luer sockets are incorporated, so that the standard infusion sets may be plugged in directly. The sockets are of different colours to allow the two channels to be identified when the tube is in place, the far ends being out of sight within the body.

The tube is made by Messrs. Portland Plastics, Hythe, Kent, and is obtainable from Messrs. Electro Surgical Instruments, 26, Eastmeads, Guildford, Surrey.

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A CHAIR FOR BRONCHOSCOPY

FOR those who prefer to perform bronchoscopy on the reclining patient, the present chair (see figure) has been designed to overcome the limitations of the dental chair.

The main advantage lies in the design of the headrest, which is under the direct control of the bronchoscopist. Lateral (7 in.), vertical ($8^1/_4$ in.), and anteroposterior (5 in.) movements are controlled by a single foot-pedal release. A system of springs and shock absorbers ensures that all movements are gentle, and that the headrest cannot slip or jerk by the pressure of the patient's head when the pedal is released.

A far greater range of movement is afforded by this headrest compared with that of the dental chair. Moreover, the greater range of backward tilt of the whole chair makes it easier to negotiate the larynx, and also allows the patient to be in a position that will satisfy the anæsthetist if a general anæsthetic is required. Transporting the chair is facilitated by the lowering of an undercarriage.

The model now being made is to have a rather shorter backrest, and one arm will be detachable.

This bronchoscopy chair was designed and made by the Dowty Group, Ltd., of Cheltenham, Glos.

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Medical Societies

MANCHESTER MEDICAL SOCIETY

Malabsorption Syndrome

ON Feb. 1 Dr. J. BADENOCH read a paper to the section of medicine on Recent Advances in the Diagnosis and Management of the Malabsorption Syndrome.

Serious deficiencies, especially of fat-soluble vitamins, can develop whenever fat absorption is impaired, and are not limited to patients with idiopathic steatorrhœa. Failure of absorption is not the sole factor in producing the clinical picture, for both the hypoproteinæmia and the disturbance in electrolytes which may arise are due at least partly to increased losses into the gastrointestinal tract, while some of the symptoms traditionally ascribed to lack of the B vitamins, notably dermatitis, may be due to the absorption of toxic metabolites from the lumen of the gut.

Some facets of the syndrome deserve wider recognition. Intestinal obstruction may arise without organic stricture of the bowel; hypoprothrombinæmia due to lack of vitamin K can produce melæna, hæmaturia, and retroperitoneal hæmorrhage, besides the more common bleeding into the skin; and magnesium deficiency can be responsible for irritability, ataxia, and muscular weakness. Megaloblastic anæmia is usually due to failure of absorption of folic acid, but in many cases there is associated deficiency of vitamin B_{12}, and this is particularly important in patients with Crohn's disease, diverticulosis of the jejunum, or the blind-loop syndrome.

Interest in the pancreas has been reawakened by the recognition that fibrocystic disease is not limited to infants but can give rise to steatorrhœa in later life, and by the description of the Zollinger-Ellison syndrome in which malabsorption may accompany the profound hypersecretion of gastric acid and also adenomas of other glands. We now know that infection of the bowel with various organisms, including the dysentery group and the staphylococcus, can give rise to steatorrhœa, that sometimes malabsorption results from mesenteric vascular occlusion, and that it can be induced by treatment with neomycin or follow therapeutic X-irradiation of the abdomen.

Estimation of fat excretion in the stools is still the best method of diagnosis; elaborate balances are unnecessary, for 95% of healthy persons on diets containing up to 150 g. of fat a day excrete less than 7 g. of fat daily in the stools. Careful radiological examination of the bowel is essential in every case, for some conditions, such as diverticulosis of the jejunum and gastrocolic fistula, can otherwise be diagnosed only by laparotomy. Biopsy of the jejunal mucosa is often useful; but subtotal or partial villous atrophy are not diagnostic of idiopathic steatorrhœa, for they may be found in other conditions where malabsorption is severe.

The gluten-free diet has revolutionised the treatment of idiopathic steatorrhœa. It must be adhered to rigidly if it is to be successful; and in children at least, when wheat flour is removed from the diet, supplements of protein, calcium, and iron are necessary. In other forms of malabsorption the traditional high-protein low-fat regimen with supplements of vitamins and minerals still has a place. Steroids are often useful and can be life-saving, but it is probably safer not to use them for maintenance treatment unless this is absolutely necessary.

Reviews of Books

Recent Advances in Human Genetics

Editor: L. S. PENROSE, M.D., F.R.S., Galton professor of eugenics, University College London; with the assistance of HELEN LANG BROWN, Galton laboratory, University College London. London: J. & A. Churchill. 1961. Pp. 194. 27*s*. 6*d*.

THIS new venture in the valuable Recent Advances series is well timed. As Professor Penrose justly puts it, the "study of heredity in man . . . has erupted violently during the last decade into a most exciting and productive activity". Of the three main new eruptions, biochemical genetics, the nuclear-sexing and chromosome-counting cytogenetic approach, and statistics, the first is represented only by a good chapter on the abnormal hæmoglobins, because Professor Penrose believes it has been well covered elsewhere. Modern chromosome work is dealt with by D. G. Harnden, and the related subject of developmental sex abnormalities by O. J. Miller, both very well. Their frequent appearances in our pages may have made these subjects very familiar to some readers, and for them the best chapter may well be a short one by J. H. Renwick on the elucidation of gene order, which makes it clear where geneticists think they are going and how they hope to get there: but all the chapters are good and worth reading. Genetics becomes more and more important, and few doctors would not read this book with profit.

Sequential Medical Trials

P. ARMITAGE, M.A., PH.D., statistical research unit of the Medical Research Council, London School of Hygiene and Tropical Medicine. Oxford: Blackwell Scientific Publications. 1961. Pp. 105. 20*s*.

IN trials of drugs the investigator often wishes to know as he goes along how the effect of the new drug compares with that of the old, and to stop the trial just as soon as a statistically significant result has been achieved or the point reached where the difference in effect is so small as not to be worth pursuing. Sequential analysis is the perfect technique for use in such trials and Dr. Armitage, who has been chiefly responsible for the introduction and development of sequential techniques in this country, has done a great service to all planners of medical trials by producing this authoritative, clearly written, brief, and stimulating book. Though he says in a preface that he has tried to provide sufficient detail to enable the medical practitioner to proceed without feeling obliged to consult a statistician, some readers may shudder at the thought that a doctor might be so rash. In fact, the book is not for those unfamiliar with elementary statistical theory and practice. It will certainly be used, however, by all statisticians consulted by medical men and by the few medical men consulted by statisticians.

Child Guidance Centres

World Health Organisation Monograph Series, no. 40. D. BUCKLE, regional officer for mental health, Regional Office for Europe, W.H.O., Copenhagen; S. LEBOVICI, consultant in child psychiatry, W.H.O. Geneva: 1960. Pp. 125. 20*s*. (Also available in French and Spanish.) Obtainable from H.M. Stationery Office, P.O. Box no. 569, London, S.E.1.

THE child-guidance centre, say the authors, is an essential element in the structure of social and medical services. It is "essentially an agency for improving the adjustment of children to their immediate environments". Even those who do not agree with this view will find this monograph interesting. The authors, a psychologist and a psychiatrist, have based their work on the lectures given at a seminar held in Lausanne in 1956 under the auspices of the Regional Office for Europe of the World Health Organisation, to study the functions of child-guidance centres and to consider ways and means of applying information gained at the seminar to the different conditions existing in various countries. The text of the monograph was submitted to all the participants in the seminar so that they could make any changes they considered necessary. Thus, a variety of opinions is reflected and the organisation of child-guidance centres is examined from many different viewpoints. There is detailed information about the location, equipment, and work of the centres and the qualifications which the authors believe should be held by members of the child-guidance team.

The value of child guidance is assumed and not discussed, and no attempt is made to provide evidence of its efficacy. In particular, there are no follow-up studies, and such as have been done are ignored—a serious omission. Although the difficulty of establishing criteria of mental health in children is mentioned, the subsequent statement "Therapy should, of course, result in a state as close as possible to that of the normal child" has, in practical terms, very little meaning. Yet the monograph is full of what "should" and "should not" be done, suggests that the ideal in any European town would be to provide for at least one child-guidance team for every 45,000 inhabitants, and discusses detailed methods of "case-finding".

The Hand

A Manual and Atlas for the General Surgeon. HENRY C. MARBLE, M.D., F.A.C.S., consulting surgeon, Massachusetts General Hospital. Philadelphia and London: W. B. Saunders. 1960. Pp. 207. 49*s*.

HAND surgery is still, and probably always will be, a specialty in which the specialists deal with only a very few of their possible patients. Upon the general surgeon, the casualty officer, and the family doctor devolves the responsibility for all but a small fraction of patients with damaged hands. Dr. Marble has chosen wisely, then, in addressing his work to general surgeons, and confining himself to common conditions amenable to straightforward methods.

His asides, and his occasional excursions into medical history, enhance the value of the book, but this is not true of some of the data included in the opening chapters. Much of this has no direct bearing on hand surgery, and many readers, seeking advice on some particular clinical issue, will feel irritated at being reminded about the pH of blood, the chemical composition of bone, or the role of adenosine triphosphate in muscle contraction. Dr. Marble advocates (p. 135) primary repair in wounds of the flexor tendons over the proximal finger segment, without indicating that the operation often fails, or that many of his colleagues would condemn it.

These objections apart, the book contains much valuable advice, concisely stated, easy to understand, and (because the author makes his points with a liberal use of line diagrams and anecdotes) hard to forget.

Fluorine and Dental Health

The Pharmacology and Toxicity of Fluorine. Editors: J. C. MUHLER and M. K. HINE. London: Staples Press. 1961. Pp. 201. 21*s*.

THIS collection of papers on the pharmacology and toxicity of the inorganic fluorides is useful, but its value would have been greater had it appeared sooner in this country—the preface is dated February, 1959.

The effect of fluorides in reducing the incidence of dental caries is not discussed, and the subtitle more adequately describes the book's scope. The important question of whether fluorine is an essential part of the diet is only touched on lightly. Though some of the papers are detailed, a more useful and up-to-date survey of the systemic effects of fluoride was published last year.[1] The same ground is also covered clearly and comprehensively by Cannell's *Medical and Dental Aspects of Fluoridation*.[2] Unfortunately, the paper on fluorides and general health is uncritical, but the lack of toxicity of fluorides at the levels recommended for the control of caries is supported by the rest of the symposium.

One aspect of fluoridation about which neither this nor any other book has much to say is the apparently greater systemic effect of fluoride ingestion in hot climates, such as India.[3]

1. *A.M.A. Arch. industr. Med.* 1960, **21**, 303-52.
2. See *Lancet*, 1960, i, 1065.
3. Singh, A., Jolly, S. S., Bansal, B. C. *ibid.* 1961, ii, 197.

The Unconscious Mind

KENNETH WALKER, F.R.C.S. London: Rider & Co. 1961. Pp. 256. 21*s*.

THE author's interest in the occult is well-known, and here, once again, he explores a few valleys in the para-scientific jungle, seeking this time to link the study of telepathy (more or less respectable nowadays) with clairvoyance, yoga, prophetic dreams, water (and other) divining, ghosts, survival after death, and—most contentious of all perhaps—radiesthesia and radionics. This is in no sense an ordinary textbook: scientific study (of hypnotic phenomena for example) and Freud receive almost no mention.

It is good to have someone who writes as well as Mr. Walker to guide us through this territory, though, as he says, he is no expert and the account adds little to subjects too much written about already from a slightly over-credulous viewpoint. The cautious and scholarly approach (such as that of West [1]) is generally preferable. Nevertheless, the evidence for some of these things is impressive, and to the rigid "scientist" the book may do some good: in the admirable words of a member of the Flat Earth Society interviewed on television, "We see it as our function to keep alive the spirit of doubt."

The First Five Minutes

A Sample of Microscopic Interview Analysis. ROBERT E. PITTENGER, M.D., director of research and psychiatric services, George Junior Republic, Freeville, New York; CHARLES F. HOCKETT, PH.D., professor of linguistics and anthropology, Cornell University; JOHN J. DANEHY, M.D., assistant professor of psychiatry, Upstate Medical Centre of the State University of New York. Ithaca, New York: Paul Martineau. 1960. Pp. 264. $6·50.

IN an introductory chapter, the authors state that their aim is to study what actually happens during the psychiatric interview. The five-minute episode recorded in this book opens the first of three initial interviews discussed by Merton Gill, Richard Newman, and Fredrick C. Redlich in their book, *The Initial Interview in Psychiatric Practice*. The second chapter gives the interview: the pages are cut horizontally, like the leaves of a horse-box door, the upper part bearing the phonetic and tape-recorded transcription, the lower part the analysis and explanatory remarks. It is claimed that the hidden significance of every turn of phrase, variation in tone or rate of speech, coughs, and throat-clearings is thus preserved for future study. The third chapter deals with the conventions of the transcription (linguistic and paralinguistic). The remaining chapters describe the methods of research used, the authors' findings, and practical applications. The book tails off into generalisations, and its conclusions are reduced to just proportions by the remark: "Nothing proposed here, of course, should be regarded as in any sense a substitute for the skilled intuition of supervisor and therapist, but only as a possible way of deriving further leads from the same data."

Arthritis and Allied Conditions (*A Textbook of Rheumatology*. 6th ed. London: Henry Kimpton. 1960. Pp. 1294. 150*s*.).—The new edition of North America's leading textbook on rheumatic disorders, edited by Dr. Joseph L. Hollander, is larger than its predecessor by 200 pages, but the quality of its new material amply justifies the increase. The text has been extensively rewritten, and nineteen entirely new chapters cover topics such as alkaptonuria and ochronosis, "stress" and the rheumatic diseases (by Hans Selye), metabolic bone diseases, cervical nerve-root compression, and amyloidosis—of which rheumatoid arthritis is now the most common cause. Dr. Hollander has more than doubled the number of contributors, and his team of distinguished physicians, surgeons, and basic scientists from the United States and Canada now numbers 39. Amid much that is praiseworthy, Dr. J. J. Bunim's concise and masterly account of the physiological and pharmacological effects of the anti-inflammatory steroids is outstanding and can be commended to anyone in search of a clear guide to the actions and limitations of these substances. Though publications as recent as 1959 are quoted, the pace of new knowledge has already outstripped the material in this and other sections. In dealing with the comparative effects of steroids and aspirin in rheumatoid arthritis the failure of cortisone to improve on the results of treatment with aspirin or to retard the development of erosive lesions in the joints is quoted as the latest information to emerge from multi-centre controlled trials in the United Kingdom. The strikingly different result of the more recent trial, in which prednisolone was used instead of cortisone, must await discussion in the next edition. The sheep-cell agglutination test, previously described in one page, now occupies, with related serological phenomena, a sizeable chapter: the discussion of the lupus-erythematosus-cell phenomenon has similarly expanded. Treatment with antimalarial drugs, barely mentioned before, is now discussed at length. The chapter on radiology is good, but could be improved by using more close-up reproductions to show the important early changes of articular disease. Assured of a place on every rheumatologist's shelf, this authoritative work will also appeal to any clinician facing the challenge of this large segment of medicine.

The Cell Nucleus (London: Butterworths. 1960. Pp. 269. 50*s*.).—This is the report (edited by Prof. J. S. Mitchell) of a symposium held in Cambridge in August, 1959. Though a very few papers deal with structure and genetics, it is overwhelmingly biochemical in content. It includes sections on the functions of the nucleolus, the synthesis of D.N.A., nuclear enzymes, and the structure of D.N.A. The contributions maintain a very even level. J. S. Sirlin's review of the D.N.A.-R.N.A.-protein chain (though we hope he did not read all of it to the meeting), John Paul on D.N.A. synthesis and X-irradiation, G. Siebert on nuclear enzymes as energy sources, and Pelc and La Cour on chromosome replication are perhaps an unfair selection of papers that caught the eye. The whole has been well edited with a good index, and very solidly produced. The report appeared 17 months after the symposium, and few reports take less time and many a great deal longer. Quick production is perhaps incompatible with the standard maintained in this volume, but many faults would be forgiven in a report that appeared within six months of the symposium, when its contents would still be news.

Biographical Memoirs of Fellows of the Royal Society (*Vol*. 6. London: The Royal Society. 1960. Pp. 295. 30*s*.).—This splendid volume contains 17 masterly obituaries, each with a portrait, on four physicists, four chemists, two biochemists, two botanists, two entomologists, one metallurgist, one biologist, and one philanthropist. They include two Frenchmen, one German, one Dane, one Dutchman, one Austrian, and one American. The biochemists are Linderstrøm-Lang and Bruno Mendel, the former specialising in histochemical problems and proteolytic breakdown mechanisms and the latter in enzymes. Medical men may be most interested in the philanthropist James Davison Rockefeller, Jr., the first president of the Rockefeller Foundation. He made so great a contribution to the advancement of science, not only of money, but of wise encouragement that the Royal Society in 1939 elected him to its fellowship as one who had rendered exceptional service to the cause of science. This singular honour by which he became a regular F.R.S. rather than a foreign member reflects the international scope and appreciation of his work. Although this volume has less interest to doctors than others in the series it is still essential for any medical library proud of its reference section.

Whitaker's Almanack 1961 (London: J. Whitaker. 1960. Pp. 1190. 21*s*.).—The *Almanack* appeared on Dec. 2, the earliest date since the war. A special section on Africa has been added to the summary of events of 1960. The new pensions' scheme, due to start on April 1, is described in detail; and the education section refers to the Crowther and Albemarle reports. By popular demand the full month-by-month record of the weather has been reinstated, and maybe next year it will read more brightly.

1. West, D. J. Psychical Research Today. London, 1954.

THE LANCET

LONDON 4 MARCH 1961

The Curriculum

THE article in this issue by Prof. DAVID RUTSTEIN, and the one by Dr. GEORGE SILVER which we published on Feb. 4, draw attention to what may well be the most important problem in medicine today—that of providing in all countries enough doctors well trained for family practice. Viewing the medical needs of the United States from different angles, both authors are convinced that, in an age of necessary specialisation, the standard of care given to the population must depend primarily not on the efficiency of the specialists but on that of the personal doctor. Appalled by the growing scarcity of doctors in this branch, they call for urgent measures to increase their quantity and to improve their quality.

Here in Britain it seems that we may have deluded ourselves that we have—and are going to have—enough doctors,[1] and certainly we have been slow to realise how time-consuming is the full personal care of patients. Yet, in contrast to the position in many countries, specialisation here has dissolved the functions of the general practitioner without removing him from the medical scene. We still retain the structure of a family-doctor service, owing perhaps to the N.H.S. fixing in the past decade the pre-existing pattern of practice in which consultants see only patients referred to them. But we cannot claim to have taken full advantage of this almost unique good fortune; and, although a start has been made (mostly by general practitioners themselves), we have not yet succeeded in defining the duties which will be required of the personal doctor. Meanwhile some of our medical schools persevere in attempts to produce general practitioners of a kind no longer needed, by a system of apprenticeship to specialists which could not succeed anyway.[2] We have every reason to consider most carefully the methods suggested by RUTSTEIN and SILVER.

Both advocate separate curricula for the specialist and the family physician. SILVER favours divergence after preclinical studies, and RUTSTEIN at entry into the medical school. Their claim that this will attract more Americans of the right kind into " general " practice is based partly on the assumption that current medical education in the U.S.A. is a disincentive to this form of work. Certainly there is evidence suggesting that the proportion of students aiming at this branch is greater in the first than in the last year of studies, though this may be due to factors other than the education given in the medical schools. The schools' policy seems to have been to inculcate a scientific attitude of mind, while also offering a short (by British standards) training in clinical technique; but it is arguable that the emphasis now so often placed on the laboratory and its procedures has in fact discouraged many students and potential students who would be good at looking after people.

RUTSTEIN's condemnation of the present policy of American medical education has, however, further significance for us. American schools have earned a reputation for the extent to which some of them deliberately expose their students to general medical clinics (presenting " undifferentiated " clinical problems), to illness in the community, to the family as such, to continuous comprehensive responsibility for patients, and to lively departments of preventive and social medicine. Many in this country are anxious to see such schemes more fully applied in our own schools, believing that in this way students will be more easily attracted to, and better prepared for, family practice. If this is not so we should know, and know why. Possibly these schemes remain rather separate from the rest of the course, so that they conflict with it rather than permeate it; or possibly it is the nature of the student rather than the type of education which mainly decides what he chooses to do.[3] Are we indeed attracting to medicine the type of person who will be interested in the work of the personal doctor of today, or do we still attract mainly the type who would enjoy being the general practitioner of yesterday, picturing himself as primarily a man of action, a do-it-all-yourself doctor? Students of this type, finding no place for the old general practitioner, might be expected to turn to a specialty.

American students lack the long grounding in clinical method customary in Britain; and if on qualifying they lack confidence (as ELLIS [4] has suggested) this might be reflected in their devoting a comparatively long time to junior hospital appointments before striking out on their own. The work of PETERSON et al.[5] in North Carolina suggested that this postgraduate experience was the most important factor in the preparation of general practitioners. In the past, postgraduate training for the general practitioner was thought in both America and Britain to be more of a luxury than a necessity, whereas in Sweden three to four years of such training has long been customary. In this country in the past three years medical schools have been endeavouring to offer their students a basic training in medicine rather than a full preparation for practice; and many have looked to America for examples of how to " instruct less and educate more ".[6] Few would disagree with RUTSTEIN's desire to reduce the learning of minutiæ and to increase the amount of clinical practice required of students. What is difficult to accept in his scheme is the idea of a curriculum based on a content of knowledge selected as " germane " to a particular professional task, and the ruthless exclusion of all clinical experience considered irrelevant to general practice or a particular specialty as the case may be. The personal doctor will meet widely

1. Laffitte, F., Squire, J. R. *Lancet*, 1960, ii, 538.
2. Ellis, J. *ibid.* p. 1041.
3. Hammond, K. R., Kern, F. Teaching Comprehensive Medical Care. Cambridge, Mass., 1960.
4. Ellis, J. R. *J. med. Educ.* 1956, **31**, 42.
5. Peterson, O. L., Andrews, L. P., Spain, R. S., Greenberg, B. G. *ibid.* 1956, **31**, no. 12, part 2.
6. General Medical Council: Recommendations as to the Medical Curriculum; p. 7. 1957.

varied clinical problems. To define and solve these he will need good clinical method and reasoning of exactly the same kind (though not in such a restricted field) as that needed by the specialist. Moreover the personal doctor will need to keep abreast of advancing knowledge over a very wide area; and he must assess this critically, just as the specialist does in his more limited sphere. It seems reasonable therefore that in the undergraduate period personal doctor and specialist should acquire the same clinical method, the same method of thought and critical attitude, and surely the same professional outlook. The content of the curriculum should not be conditioned merely by supposed relevance to the future professional task. Besides, how many really know at the start of training for which branch they will be best suited?

The old system of medical training broke down because every student was expected to learn everything. We have come to realise that it is not so much knowledge as the power to utilise knowledge that the student must acquire. But not all students can be expected to acquire this power by a single route: all of us learn more easily in those fields which interest us most. Thus the rigid insistence on passage of all students through all departments should cease, and gaps in knowledge be made good in the postgraduate period. If the student does not learn to evaluate data critically, then such gaps (and there are bound to be many whatever the curriculum) will probably remain, and he will be largely denied the mastery of new data.[7] The newer system may result in a student specialising fairly early in his course; but his curriculum will be based on his own needs in education, and not on a content of fact, theory, and technique deemed appropriate to the current practice of his future specialty. Such a system will involve extension of postgraduate training, which fortunately in this country (unlike the U.S.A.) is on the whole adequately financed. Only in general practice have we so far failed to devise a satisfactory system of properly paid postgraduate training; and until we have done so we are unlikely to produce personal doctors who are thoroughly prepared for their job. Whether we produce enough of them depends greatly on the nature of the men and women who are being attracted to medicine. Any light which the inquiry now being conducted by ASME throws on the professional ambitions of medical students and their reactions to training should be of great value.

Pavlov or Freud

PSYCHOANALYTIC theories of the cause and treatment of the neuroses have always been sharply criticised. Among the more challenging of the present-day critics is Prof. H. J. EYSENCK, who prefers the "learning theory" approach based on PAVLOV's experiments on conditioning. In his view it offers an ætiological explanation and method of treatment which could supplant psychoanalysis. According to an authoritative statement of the view of the learning theory school,[8] neurosis is not a disease process but a collection of symptoms which are bad habits acquired as conditioned reflexes. EYSENCK's own contribution has been to offer a hypothesis why these should have developed in some people rather than others.

People, he suggests, develop conditioned responses at different speeds and with different degrees of tenacity according to their personality. All neurotic symptoms are either surplus conditioned reactions (as manifest in dysthymics) or deficient conditioned reactions (as in hysterics and psychopaths). He accepts the analytic theory that underlying anxiety (viewed as a drive-producing autonomic response) is crucial, and that motor symptoms (such as tics and compulsive movements) arise because of their drive-reducing properties. He regards underlying unconscious conflict as an unproven hypothesis which can be disregarded in treatment. If the symptoms are removed (and this must of course include anxiety) the neurosis is cured, and symptom substitution is not expected to occur.

The term "learning theory" usually means learning by conditioned reflex, but it can have other applications,[9] and there is enough controversy over detail to lead to disagreement both over hypothesis and interpretation of results. The chief merit of the learning theory is that, unlike much analytic writing, it has produced fruitful hypotheses open to refutation or confirmation. Discrepancies in learning theorists' work already suggest that the evidence in favour of parts of EYSENCK's hypotheses is not clear-cut.[10]

For instance, it now seems clear that, as forecast,[11] dysthymics fall on the introverted side of normal and psychopaths on the extroverted. But, contrary to expectation, neither hysterics [12] nor recidivist criminals [13] differ from normals. However, some recidivists develop reflexes more easily than normal people; perhaps they are reacting to a less favourable environment. They were also found to be significantly more neurotic and rigid than normal people, and FIELD and BRENGELMANN [14] have suggested that rigidity of personality is at least as important as extroversion and neuroticism in explaining how different people vary in acquiring reflexes.

Clearly the situation is complex; experimental work is still at a preliminary stage, and many of the difficulties in repeating results could be partly explained by unsatisfactory psychiatric nomenclature.[15] Diagnosis is still unreliable,[16] and terms are used in different ways by different clinicians. Learning is obviously an important part of development, and conditioning has been accepted by psychoanalysts as important in the development of at least some disorders.[17] The theory may need extensive modification, yet, "while derivations are not always unambiguous and logically rigorous, in the hands of the originator, the theory has provided a productive source of hypothesis and a stimulus to research".[10]

Treatment is largely based on HULL's theory which expresses in mathematical terms the factors determining the formation and extinction of conditioned reflexes.

7. Ellis, J. *Lancet*, 1960, ii, 1041.
8. Behaviour Therapy and the Neuroses. Editor: H. J. Eysenck. London: Pergamon Press, 1960. Pp. 480. 63s.
9. Thorpe, W. H. Learning and Instinct in Animals. London, 1956.
10. Storms, L. H., Sigal, J. J. *Brit. J. med. Psychol.* 1958, **31**, 228.
11. Eysenck, H. J. Dynamics of Anxiety and Hysteria. London, 1957.
12. Sigal, J. J., Star, K. H., Franks, C. M. *J. abnorm. (soc.) Psychol.* 1958, **57**, 143; Eysenck, H. J. *ibid.* p. 250.
13. Field, J. G. Report to the Prison Commission. 1960.
14. Field, J. G., Brengelmann, J. C. *J. abnorm. (soc.) Psychol.* (in the press).
15. Stengel, E. *Proc. R. Soc. Med.* 1960, **53**, 123; *Lancet*, 1960, i, 158.
16. Brooke, E. *Proc. R. Soc. Med.* 1960, **53**, 128.
17. Alexander, F. Fundamentals of Psychoanalysis. London, 1946.

The chief methods used are reciprocal inhibition, negative practice, aversion therapy, and positive conditioning.

WOLPE [18] early used reciprocal inhibition on the grounds "that if a response incompatible with anxiety can be made to occur in the presence of anxiety-evoking stimuli it will weaken the bond between these stimuli and the anxiety responses".[19] Reciprocal inhibition has been especially used in phobic patients.[20] MALLESON has used a rapid technique in patients with examination panic,[21] as had GORESKY some ten years earlier in his Canadian general practice.[22] According to KNIGHT DUNLAP's ingenious method of negative practice, first expounded in 1932 [23] but little used until lately, the patient actively and consciously practises the habits of which he wishes to rid himself. Thus the deliberate and repeated voluntary practice of an involuntary tic may reduce or eliminate the symptom.[24 25] In aversion therapy the symptoms to be eliminated are linked with an unpleasant experience (typically the injection of apomorphine or the administration of an electric shock). It has been used in the treatment of alcohol addiction and sexual perversions.[26 27] In positive conditioning the aim is to develop a normal reflex which the patient failed to acquire—as in treating enuresis by an electric pad and alarm-bell.

It would be nothing new for a successful treatment to be based on a fallacy, and, though theory and therapy are linked by its exponents, the clinical application of the learning theory should be assessed independently of the theory itself. One advantage claimed for the method is brevity—an average of some 30 treatments in WOLPE's series; but this is a not inconsiderable time, longer, for example, than that spent in outpatient treatment at a general psychiatric [28] or psychotherapeutic clinic.[29] Again, WOLPE claimed 90% recovery in his large series of treated cases, which seems distinctly better than that achieved by other methods.[30] But patients who had not had an "adequate" amount of therapy were excluded; and such comparisons mean little when the groups are heterogeneous and equated for neither "seriousness" of disorder nor duration of symptoms. Nor was there any comparisons with control—the very sin for which learning theorists sometimes castigate psychoanalysts.

Rather than attempt an overall view of the value of the method it might be more useful to look at the results in different disorders, and EYSENCK [8] has now brought together most of the published reports of patients treated by conditioning methods and the different techniques and their applications. In most the treatment was experimental and no attempt was made to compare the efficacy of different methods.

Results are often conflicting: LIVERSEDGE and SYLVESTER's success in treating writer's cramp [31] must be set against the poorer results found by BEECH.[32] There have been few controlled trials, even in the treatment of alcohol addiction by aversion therapy and of enuresis by pad and bell. The evidence, such as it is, suggests that, though in alcohol addiction results may often be less good than those achieved by other methods,[33] the conditioning of enuresis is usually successful.[34]

We do not yet know how effective conditioning therapy is, nor when it should be tried. It is surely too early to talk of results being "permanent" [35] or to speak of the "cure" of homosexuality by conditioning.[36] As LEIGH has pointed out,[37] learning theory is now in the state in which psychoanalysis was in 1903, when cases were being published of the cure of Frau So-and-so. As GLOVER emphasises,[38] several techniques are often combined with conditioning methods, and CASE points out that "unless social adjustment is undertaken in cases displaying severe social maladjustment, the patient will not entirely succeed in freeing himself... (of the symptom)".[39] Controlled trials are needed in which the relative value of conditioning therapy in different disorders is compared with that of other methods. But if not yet a proven form of treatment, it already offers important working hypotheses for practical forms of therapy in disorders often resistant to treatment, and these methods deserve to be tested.

Aircraft Accidents

MAJOR accidents to large passenger-carrying aircraft are happily rare, but when they occur they are usually catastrophic. In the first eleven days of February there were no fewer than nine railway accidents in the United Kingdom; but all combined resulted in less loss of life that a single serious air crash. It is not only the high proportion of fatal casualties but also the peculiar horror of the scene which shocks the public. The effects of impact at high speed and the fire which consumes the wreckage not only make rescue difficult but also destroy evidence on the cause of the accident.

The most dangerous part of an aerial journey is when the aircraft is just above the ground, either taking off or landing. At this time of transition, the aircraft is vulnerable because the pilot has only a small margin of control with which to counteract anything unexpected, whether due to equipment failure or to an error of judgment. Adverse circumstances, such as darkness or bad weather, increase this vulnerability. Jet aircraft have a critical attitude for take-off, and this attitude is more difficult to judge at night: the speed for take-off and landing must be maintained between narrow limits which vary with the load, the length of the runway, and the weather

18. Wolpe, J. Psychotherapy by Reciprocal Inhibition. University Press, 1958.
19. Wolpe, J. *Arch. Neurol. Psychiat.* 1954, **72**, 205; *in* Behaviour Therapy and Neuroses, p. 88.
20. Freeman, H. L., Kendrick, D. C. *Brit. med. J.* 1960, ii, 497.
21. Malleson, N. *Lancet*, 1959, i, 225.
22. Goresky, V. *Vancouver med. Bull.* January, 1948.
23. Dunlap, K. Habits, their Making and Unmaking. New York, 1932.
24. Yates, A. J. *J. abnorm. (soc.) Psychol.* 1958, **56**, 175; *in* Behaviour Therapy and Neuroses, p. 236.
25. Jones, H. *in* Behaviour Therapy and Neuroses, p. 250.
26. Freund, K. *ibid.* p. 312.
27. Raymond, M. J. *Brit. med. J.* 1956, ii, 854; *in* Behaviour Therapy and Neuroses, p. 303.
28. Hare, E. H. Bethlem Royal and Maudsley Hospital Triennial Statistical Report, 1955–57.
29. Haddock, J. N., Mensh, I. N. *Psychol. Rep.* 1957, **3**, 109.
30. Eysenck, H. J. *J. Cons. Psychol.* 1952, **16**, 319.
31. Liversedge, L. A., Sylvester, J. D. *Lancet*, 1955, i, 1147; *in* Behaviour Therapy and Neuroses, p. 327.
32. Beech, H. R. *in* Behaviour Therapy and Neuroses, p. 349.
33. Wallerstein, R. S., Chotlos, J. W., Friend, M. B., Hammersley, D. W., Perlswig, E. A., Winship, G. W. Hospital Treatment of Alcoholism. London, 1957.
34. Jones, H. *in* Behaviour Therapy and Neuroses, p. 377.
35. Eysenck, H. J. Granada Lecture, 1960.
36. Eysenck, H. J. *Proc. R. Soc. Med.* 1960, **53**, 504.
37. Leigh, A. D. *in* symposium at Royal Society of Medicine, Jan. 12, 1960.
38. Glover, E. *Brit. J. med. Psychol.* 1959, **32**, 68.
39. Case, H. W. *in* Behaviour Therapy and Neuroses, p. 207.

conditions. When the visibility is poor, the pilot has to make a rapid transfer from his intruments to visual flight and to interpret instantly and correctly approach lighting which may be in sight for only a second or two before his wheels meet the runway. This transfer of attention, the refocusing of vision and the reorientation of the judgment, are the most difficult parts of a pilot's task. They require great ability, constant practice, physical wellbeing, and also a well-designed cockpit in which the instruments and the controls are carefully sited.

Unfortunately instrument design has not progressed as fast as the performance of the aircraft. Altimeters and airspeed indicators which have to register the wide height and speed ranges of jet airliners are no more accurate, and are not less but more difficult to read, than the instruments which were just adequate fifteen years ago. It is still necessary for the pilot to raise his eyes from the instrument panel to the windscreen and change his accommodation from near to far vision in the last moments of his approach, just as it was when his aircraft landed forty miles an hour slower and needed half the landing run of the modern airliner. It may soon be possible to improve so unsatisfactory a situation. The instrument dials may be projected on to the windscreen, or the pilot may be able to watch the ground by electronic means; or, in the new British airliners, the landing may be entirely automatic. Measures of this sort, which will add greatly to flight safety, are urgent.

For the professional aviator, though bad-weather landings are the greatest strain, the general load of worry and responsibility is increasing. The higher and the faster the aircraft flies, the more serious any departure from the normal. The experienced pilot never relaxes his attention. His eyes are occupied in a ceaseless scan of flight instruments, engine instruments, pressurisation indicators, warning lights, and the sky around. The situation is never static, and he aims to detect an incident in the few seconds before it becomes an emergency, or an emergency before it becomes an accident. He has constantly to guard against fixing his attention on one aspect of the flight: an instrument which shows some malfunction exerts a hypnotic effect which can interrupt his methodical scan long enough to endanger the aircraft. Many of the "near-misses" from head-on collision are due to some preoccupation of this sort; many seemingly inexplicable accidents have this same cause.

With the increase in aircraft performance, traffic has increased notably; and the risk of mid-air collision, the consequences of which are absolutely disastrous, has forced all civil aviation authorities to adopt numerous regulations, which are strictly enforced, to ensure safe separation between aircraft. These regulations, which are intended for the protection of crews and their passengers, unhappily divert the pilot's attention from his primary task; not only must he insist on meticulous height-keeping and navigation, but he is occupied with constant radio calls to report his position to the ground control, sometimes as often as once a minute. Air-traffic regulations, necessary as they are, can themselves have dangerous effects.

The safety of aircraft depends very much on the air-traffic controllers, who have a special responsibility to prevent collisions. The closing speed of two jet aircraft approaching one another may be 1200 m.p.h. or more. At great altitude, the eye suffers from a physiological myopia because of the emptiness of the visual fields outside the aircraft and the near accommodation for the instruments in the cockpit. It is thus difficult to see another aircraft at more than about 3 miles; hence at these speeds there is less than 9 seconds to appreciate the danger and to complete evasive action. The traffic controllers, by constantly plotting the position of all aircraft and by radar surveillance, help to avert such situations; but they do their important work under very exacting conditions. Doors and windows are usually shut against the noise of aircraft nearby, there is low illumination so that radar tubes can be accurately read, the electronic equipment generates considerable heat, and there are numerous radio channels to be listened to and answered. In many control centres the conditions could scarcely be worse for work which requires clear thinking, good judgment, and rapid decision.

Such is the demand on the skill, prudence, and judgment of airmen that lapses are understandable; but the rarity of serious accidents shows how well these men meet their responsibilities. When an accident does occur, inquiry boards often have little evidence to show the true cause. They are perhaps a little too ready to conclude that the pilot was to blame. The epitaph "pilot error" is convenient, but seldom convincing to colleagues who knew the man and not always satisfactory to those who dislike the thought that administrative convenience may cover up injustice. Even if the pilot has made an error—and, in one sense, an accident is always due to pilot error—what was the real cause? What the combination of circumstances—poor design, equipment failure, or faulty information—that proved an intolerable load? We need to know, for a similar combination might occur again.

Every effort, no doubt, is made by airline operators to prevent accidents, but it is legitimate to wonder whether they do all they could to lessen the seriousness of accidents when they occur. From time to time people lose their lives when an aircraft crashes at low speed. They are killed by impact against the seat in front or, being unconscious or incapacitated, are burned to death. Many of these deaths could be prevented by the simple expedient of seating the passengers facing aft on seats properly stressed and anchored to the floor,[1] and by the use of less inflammable fuels, oils, and hydraulic fluids. For every aircraft that comes down in the sea, several crash on land: yet, though the air-transport regulations insist that inflatable waistcoats shall be carried and demonstrated on every flight across the ocean, they do not provide for those safety measures which are far more likely to be put to the test.

Last December 136 people were killed when two airliners collided and crashed on a New York street.

1. See *Lancet*, 1959, i, 1275.

The next day 53 people were killed when a Service transport crashed on a street in Munich. There have been very few similar incidents in the history of aviation; but in ten years' time the crash of a large aircraft may be very much a matter of public health. It seems likely that atomic engines will power commercial as well as military aeroplanes, because nuclear energy will at last resolve the design problem of balancing range against pay-load. Free of the necessity to carry enormous quantities of fuel, the nuclear aircraft will have almost unlimited range. But if it should crash, and if its nuclear material should be scattered or catch fire, the local radiation hazard would be severe. The operators of such aircraft may be forced to use coastal aerodromes away from populated areas or to revive the moribund flying-boat. A more revolutionary, though by no means impracticable, alternative is to keep the nuclear aircraft almost permanently in the air, except for periodical overhaul on the ground. Air-refuelling is already a standard technique in the R.A.F. and U.S.A.F. There seems no reason why crews, passengers, and supplies should not be taken to the nuclear aircraft in flight by short-range, conventional tenders which would not need vast runways and which could be built for safe operation near the ground rather than for speed in the air.

Annotations

EXTRAPULMONARY INFLUENZAL INFECTION

INFLUENZA results from attack by the influenza virus on the cells of the upper respiratory tract and bronchial tree; but sometimes the virus descends further, and some workers believe that it may cause true virus pneumonia.[1 2] The virus might be expected to penetrate beyond the alveolar cells and enter the capillaries; but, in fact, the virus is not isolated from the blood-stream in an attack of influenza, and the generalised symptoms are usually ascribed to "toxic" effects from the absorption into the blood of the breakdown products of infected cells.

Some cases of encephalitis associated with influenza since the Asian influenza (A2) virus has become prevalent have been postinfectious and probably of the type which can follow any acute infection; but others have coincided with the virus infection, and virus was isolated from the brain in such a case.[3] Kaji et al.[4] recovered influenza virus from the spleen, lymph-nodes, liver, and other tissues in 3 fatal cases. Since they took scrupulous care to avoid contamination, their results suggest that, at least in severe cases, the Asian influenza virus may occasionally circulate in the blood in an infectious form. In very young animals the virus seems to propagate in a wide range of tissues [5]; and it also spreads quite readily through the body, so that giving a "pneumotropic" strain of influenza virus by subcutaneous or intraperitoneal injection may lead to a fatal infection of the lungs.[6] In adult mice intravenous administration of very large doses of influenza virus results in pulmonary infection, which, however, does not ensue from peritoneal administration.[7] It is unlikely that the respiratory tract of man ever becomes infected secondarily to infection elsewhere in the body.

A report from the U.S.S.R.[8] refers briefly to studies on 10 newborn (under 48 hours old) and 1 stillborn child delivered in Kiev during the influenza A2 epidemic of 1958–59. Influenza virus was isolated from the lungs, in which pathological changes compatible with influenza were found. The Russian workers then inoculated intranasally with a large dose of influenza virus 10 pregnant mice which were within 3 or 4 days of delivery. Embryos or baby mice were examined either just before natural delivery or after nursing for up to 4 days on healthy foster-mothers. Virus was detected by egg inoculation in the fœtal membranes and amniotic fluid of 6 out of 10 mothers; in 19 of 29 baby mice or embryos virus was detected both by hæmagglutination and by egg inoculation (though the exact method of obtaining material from the babies for virus tests is not described). Influenza-like histological changes were found in the lungs; and the changes were most pronounced in the animals which survived for a few days, when virus isolation was less frequent.

If we assume that the human fœtus or newborn infant is likely to be highly susceptible to influenza, and that influenza virus may circulate in the blood, then possibly infants may be born with congenital abnormalities or with active disease because their mother was infected with the virus. Coffey and Jessup [9] concluded that, during the early waves of A2 influenza in Ireland, congenital abnormalities had resulted from infection of pregnant women; but in the U.S.A. no evidence of such a sequence was found. Doll et al.[10] have published the results of a prospective survey in which again no connection could be established between influenza in the mother and stillbirths or congenital abnormalities. Such studies are difficult because fairly large numbers must be followed. Moreover, ideally the diagnosis should be established or excluded by laboratory tests. In the survey by Doll et al. these were not possible, but this survey excludes the possibility of a large adverse effect. Doll et al. have, however, found some evidence from the Registrar General's statistics for Scotland that an increase in the frequency of the delivery of anencephalic fœtuses was correlated with influenza A2 infection at a time when the mothers of the fœtuses were probably about 2 or 3 months pregnant.

All these new findings do not upset the established conceptions of the pathogenesis of influenza in man, but they do suggest that occasionally influenza-virus infection may be followed by viræmia and by congenital defects or intrauterine infection of a baby.

NEUTRON ACTIVATION ANALYSIS

QUITE often these days new techniques of importance to medical science are devised in other fields—perhaps especially physics. One such technique is neutron activation analysis. A sample of material is irradiated with neutrons; these neutrons will interact with many kinds of atom, making them radioactive. These can then be identified and estimated by study of the radiations emitted.

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2. Louria, D. B., Blumenfeld, H. L., Ellis, J. T., Kilbourne, E. D., Rogers, D. E. *J. clin. Invest.* 1959, **38**, 213.
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10. Doll, R., Hill, A. B., Sakula, J. *Brit. J. prev. soc. Med.* 1960, **14**, 167.

This technique is not really so difficult and cumbersome as it sounds; and it is remarkably sensitive. As, Br, and Se, for instance, are measurable in concentrations of one part per thousand million, and a dozen other elements in concentrations up to one part per ten million.[1] The different elements may be identified partly by the kind of radiation emitted and partly by the observed rate of decay, although (particularly with mixtures of many elements) chemical separation may also be necessary. Many of the elements which react in this way are important in biology and medicine. From 10 ml. of serum it is possible to estimate not only Na, K, Cl, and P, but also Ca, Cu, Zn, Mg, Co, Mn, Br, and I.[2] Of the trace elements, arsenic has already been widely studied.[3] Often the analysis can be carried out without destroying the specimen examined—a particularly convenient feature where items of historical or legal importance are concerned. Recent tests suggest that Erik XIV of Sweden, who died some four hundred years ago in mysterious circumstances, was poisoned with mercury.[4]

Easy and quick access to a source of neutrons is essential. As yet, only a few hospitals have their own nuclear reactors—for which we are profoundly thankful—and, although a linear accelerator or a large source of radium mixed with beryllium can be used,[5] in practice it is usually necessary to have a reactor close at hand. Accordingly the hospitals which could use this technique are limited to certain areas, since many of the radioactive materials to be studied can no longer be measured even an hour or two after withdrawal from the reactor. Thus, although the applications of activation analysis grow apace, and international conferences have been held for the pooling of ideas,[4] at present it looks as though the main applications may not be in biology and medicine. Further, for good or ill, the four elements of outstanding biological importance—C, O, H, and N—do not normally become radioactive in this way and are therefore outside the scope of this technique. Were this not so, their radioactivity might be so great as to prevent the measurement of trace elements.[6] Thus for medical research this interesting new technique seems promising but its applications are likely to be somewhat restricted.

DIABETES AND ENDOMETRIAL CANCER

ONCE again attention has been drawn to the concomittance of diabetes and carcinoma of the uterus. Benjamin [7] seeks to explain the difference between the findings of those who, like Benjamin himself, report that diabetes is more than usually prevalent in patients with endometrial cancer,[8–11] and of those who disagree.[12–14] As Way [10] pointed out, carcinoma of the corpus uteri is associated with the insulin-resistant or so-called senile type of diabetes, in which the fasting blood-sugar level may be almost normal and the urinary threshold for glucose high. And Benjamin remarks that those who have found that more than 20% of patients with endometrial cancer had diabetes all established this diagnosis by the glucose-tolerance test; whereas those who have found diabetes in a much lower proportion of such cases investigated, at most, the fasting blood-sugar level. In fact, of Way's series, investigated by the glucose-tolerance test, in many cases where the diagnosis was originally established by the glucose-tolerance test, clinical diabetes has since supervened.[14]

Benjamin compares the prevalence of diabetes in cases of cancer of the body of the uterus with that in cases of cervical cancer and of controls of the same age-group with neither disease. He found that 14 (28%) of 50 patients with cancer of the body of the uterus had diabetes, compared with 6 (12%) of 50 patients with cervical cancer and 13 of 100 controls.

Way [10] suggested that the coexistence of the two diseases might be due to a common factor—namely, pituitary disorder. We hope that gynæcologist, physician, and biochemist together will elucidate this question.

GALACTOSÆMIA

GALACTOSÆMIA is one of the most fully elucidated inborn errors of metabolism. Its clinical features—galactosuria, liver enlargement followed by cirrhosis, cataract, aminoaciduria and proteinuria, retardation of physical and mental growth, and commonly death in infancy—are well established. The specific enzyme deficiency is that of a nucleotide transferase which catalyses the conversion of galactose-1-phosphate to glucose-1-phosphate. The deficiency of this enzyme can be shown in red blood-cells and in liver. The disorder, like most other inborn errors of metabolism, is apparently due to a recessive mutant gene—though, as in many other such conditions, the mutant gene is not fully recessive but may manifest itself to some degree in the heterozygote. Holzel and Komrower [1] showed that some of the parents of children with this disorder had an abnormal galactose-tolerance curve; often this was found in only one parent, although both must be presumed to be heterozygous for the gene concerned. Hsia et al.[2] found that about half the heterozygotes could be detected by estimating the level of the enzyme in red blood-cells. Mild clinical manifestations have been reported in probable heterozygotes—for example, siblings of patients with a trace of reducing substance in the urine [3 4]—while two groups of workers [5 6] have each recorded a case in which a paternal grandfather was intolerant of milk.

Hugh-Jones et al.[7] have described a family which illustrates well both the recessive mode of inheritance and clinical manifestation in the heterozygote.

The index patients were a brother and sister with typical clinical and biochemical findings, except that both were relatively mildly affected; the diagnosis was made in the boy at

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the age of 9 years and the girl at the age of 5, and there was little mental retardation. Two sisters of these children were clinically healthy, though enzyme and tolerance tests indicated that they were probably heterozygotes. Their mother, a woman of 34, had been known to have renal " glycosuria " for the past ten years, and, when the diagnosis had been established in her children, it was found that the reducing substance was galactose. She had diarrhœa and headaches if she took milk. Two of the mother's sisters were known to have had sugar in the urine when pregnant, and two brothers constantly had " glycosuria ". There was one further sib—a woman with no reducing substance in the urine. Enzyme tests showed that all the sisters and brothers of the mother were heterozygotes, the highest level of enzyme being in the sister who was least affected.

The explanation of these remarkable findings lay in the mother's father, born in 1894, who had been thought to have diabetes mellitus for sixteen years. He had cataracts and an enlarged firm liver, but he was of above average intelligence and was reasonably healthy. The reducing substance in his urine was galactose, and his enzyme levels and his galactose-tolerance test were in the range of those homozygous for galactosæmia. It is understandable, therefore, that all his children should be heterozygotes. For any grandchildren to be affected it is, of course, necessary that one of his children should have married a carrier; the father of the two affected children, though one of a large healthy family, had an enzyme level which was well down in the range for heterozygotes, although the galactose-tolerance test was not abnormal.

This family emphasises a lesson that is also being learnt from phenylketonuria—that the range of clinical manifestations, even of the homozygous state of a recessive mutant gene, may be very varied. But the unusual mildness of the condition in the grandfather, and the unusually high incidence of galactosuria in his heterozygous children, raises the question whether, on this side of the family, one of the genes responsible was a slightly different mutation at the same gene locus.

AN AMERICAN STUDY OF ALCOHOLISM

IN the U.S.A. alcoholism ranks as " Public Health Problem No. 4 ", and all over the country official programmes have been planned to cope with it. From California comes an account of a *Study of Community Concepts and Definitions* [1] based on an analysis of two-thirds of 157 interviews with community leaders. The first objective was to establish a means for earlier detection of those who are at risk of falling victims to alcoholism. The selection of community leaders was neither random nor representative, but was aimed at obtaining as great a diversity of replies as possible. Those selected were asked how they identified problem drinkers and early alcoholics, and what they regarded as the conditions responsible for excessive drinking. The results of this preliminary study suggested that the warm climate, the local wine industry, a tradition of widespread drinking of alcoholic beverages, and the great number of rootless persons in the population were all important factors; and among those named as especially prone to alcoholism were the emotionally unstable, those with many family or other problems, and those with a poor background such as a broken home. On the whole this well-conceived and critical study supports popular present-day beliefs; but, as the authors rightly claim, " although the social conception has probably been well known to informed persons . . . the many details of the picture . . . have never before been collected and assembled into an empirically grounded, interrelated social conception ".

A Prospective Follow-up Study [1] began in 1956 with three groups of alcoholics—numbering over 1000 in all—who were starting treatment. In composition these groups resembled those reported in other investigations, including some in this country. Thus the median ages were 43–46 years; there was a preponderance of men; and the proportion of widowed and divorced was at least twice as large as in the general population. But in contrast to the findings in British studies, the proportion of labourers was high, that of white-collar workers low. Compared to the general population the alcoholic groups had a poor, " depressed " status: for example, mortality was twice as high, about 1 in 10 dying from liver cirrhosis, and 1 in 3 from violent causes; and almost half the drivers among the alcoholics were in a three-year period convicted of violations of the vehicle code. Of the three groups one was treated from the start in a mental hospital; and of the other two groups the proportion admitted to a mental hospital in a single year was 8%, compared with 0·2% of the adult civilian population in the State. The generally poor status manifested itself also in low occupational and educational levels, marital disruption, poor health, and economic and social complications.

All information about post-treatment adjustment was obtained from personal field interviews carried out three to twenty months after treatment, when 7 out of 10 members of the original groups were successfully traced and interviewed. About 40% had been employed at least half the time since treatment; about the same proportion had not drunk heavily again; and 70% had managed to keep out of hospital. Improvement was greatest in regard to health, absenteeism from work, and participation in religious activities. But during the period of readjustment many alcoholics continued to live in " the transient kinds of living quarters that shelter unattached, indigent males " —which again brings out the advisability of establishing half-way houses for treated alcoholics.

Criminal Offenders and Drinking Involvement [1] describes a preliminary study which showed that crimes committed shortly after drinking were associated with much personal risk (homicide, assault, car theft), whereas " problem drinkers " usually committed offences for economic gain (passing bad cheques, forgery, and, again, car theft).

These reports are tentative and incomplete: several years must elapse before the duration of improvement in drinking habits can be evaluated—although, as the authors point out, " drinking is but one of many factors that must be accounted for in producing a reliable measure of adjustment ". But even these preliminary accounts contain a wealth of useful material about the design of such studies, community attitudes to alcoholics, treatment successes and failures, and the relation between " problem drinking " and crime.

1. Reports of the Division of Alcoholic Rehabilitation of the Department of Public Health (State of California). Publication no. 1: A Study of Community Concepts and Definitions (part 1). Publication no. 2: Selected Aspects of the Prospective Follow-up Study (a preliminary review). Publication no. 3: Criminal Offenders and Drinking Involvement (a preliminary analysis).

Sir THOMAS FAIRBANK, consulting orthopædic surgeon to King's College Hospital and consulting surgeon to The Hospital for Sick Children, Great Ormond Street, died on Feb. 26 at the age of 84.

Medical Education

PHYSICIANS FOR AMERICANS

Two Medical Curricula: a New Proposal *

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A PRIME responsibility of medical schools is to educate enough of the different kinds of physicians needed to provide adequate medical care for the people.

If this assumption be accepted, it can easily be demonstrated that the medical schools of the United States in 1960 are not meeting this responsibility and that they face a grave problem which must be solved. The facts are well known from many recent studies [1–3] and can be summarised briefly.

THE INCREASING SHORTAGE

The number of physicians now practising in the United States, and those to be graduated during the next decade, do not and cannot meet the needs of our growing and changing population if demands for medical service continue at the present level. At a rate of five physician's visits per person per year, a population estimate of over 200 million by 1975, and the medical-school expansion programme now projected, it will be impossible to maintain the present physician/patient ratio of one to 750. With an increasing proportion of very young and very old people in our population, and with most general physicians overworked at the present time, it appears reasonable to try to maintain this ratio.

The growing deficiency is greater among those providing general medical services—i.e., general practitioners, internists, and pædiatricians. The drop in the general physician/patient ratio from 1 per 1100 to 1 per 1700 people in the United States from 1931 to 1957 was abrupt and is continuing.[2] This trend towards the disappearance of the general physician is nation-wide. It is shown by the complete lack of physician's services in some rural areas and the shift toward specialty practice in urban areas.

The suggestion has often been made that the internist will be the general physician of the future. But with our present programme of medical education the number of internists providing personal health services cannot meet the need either now or in the foreseeable future. There is less than one internist for every 14,000 people in the United States. Many of these internists are in a subspecialty or in full-time positions in industry, in the medical schools, or in Veterans' Hospitals. Internists are rare in rural areas and over one-quarter of them practise in the two States of New York and California. Assuming that they were evenly distributed throughout the country, that they were all in general practice, and that pædiatricians would continue to be educated at the present rate, it is estimated that by 1975, if general practitioners continue to disappear at the 1931–57 rate, we will need six times as many internists as are now in practice in the United States to regain the general physician/patient ratio of the early 'thirties (1 per 1100 of the population).

When a patient has no general physician, lack of continuity in his medical care is inevitable. His health will not be properly supervised and gaps will occur in his care when he is ill. Moreover, he is often confused by conflicting information given to him as he goes from specialist to specialist or is referred from one service to another in our highly compartmentalised hospitals.

A whole host of ancillary medical personnel has been created to perform tasks once considered to be in the province of the general physician. These include public-health nurses, medical social workers, nutritionists, occupational and physical therapists, clinical psychologists, and vocational rehabilitators. The paramedical professions make great contributions to medical care, but their very creation and existence have increased the need for a general physician to select wisely and coordinate their services for the benefit of the patient.

The inadequate number of physicians graduating from our medical schools has forced us to turn to graduates of medical schools in foreign countries to fill about one-quarter of our internships and residencies (8400 of 35,000). Indeed, there are more foreign physicians in our hospitals than graduate each year from all medical schools in the United States. Most of these foreign graduates come from the Philippines, Turkey, Mexico, Iran, Korea, Greece, Japan, and India—countries whose medical standards are not comparable to our own.† Actually in 1959, there were over 2500 Philippine interns and residents in our hospitals, an average of about 500 from each of the five proprietary medical schools in that country.[4] ‡ One might wonder whether physicians coming from these countries are on the average more capable than the students who flunk out of our medical schools. Examinations by the Educational Council for Foreign Medical Graduates will eliminate the more incompetent of these, but the need for interns and residents will then become greater.

As a result of the inadequate number of physicians graduating from American medical schools, an increasing proportion of foreign interns and residents are being licensed to practise in this country. Those licensed have increased from 458 in 1951 to 1316 in 1958.[2] In other words, about one out of every six doctors, newly licensed in the United States in 1958, was a graduate of a foreign medical school. Many of these foreign physicians go into general practice.

In effect, we discourage American students from obtaining a medical education leading to general practice. To take their places, we encourage graduates of low-grade foreign medical schools, whose standards resemble the

* Based on an address at the Institute of the Association of American Medical Colleges, on Medical Services and Medical Education—Today and Tomorrow, at Hollywood Beach, Florida, on Nov. 2, 1960. This address, with discussion by participants, will appear as part of the entire Proceedings of the Institute to be published in 1961 by the Association of American Medical Colleges, of Evanston, Illinois, in a volume entitled *Medical Services and Medical Education: Report of the Eighth Teaching Institute.*

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2. Physicians for a Growing America: report of the Surgeon General's Consultant Group on Medical Education (Frank Bane, chairman). P.H.S. pub. 709, U.S. Government Printing Office. Washington, 1959.
3. Federal Support of Medical Research: report of the Committee of Consultants on Medical Research (Boisfeuillet Jones, chairman). U.S. Government Printing Office. Washington, 1960.

† This educational experience could be beneficial to the foreign physicians. But positions in the better teaching hospitals are preempted by our own medical graduates. For the most part, the foreign intern or resident accepts appointments in non-teaching hospitals where there is relatively little formal instruction or supervision. As an educational experience it leaves much to be desired. We should establish a planned postgraduate educational programme for the graduates of these foreign medical schools.

‡ In contrast, the one non-proprietary medical school, the University of the Philippines, College of Medicine, graduates only about 100 students per year; but few of these come to the United States.

4. Barrera, B., dean and professor of pathology, University of the Philippines, College of Medicine. Personal communication.

pre-Flexner schools in the United States. This brings us face to face with the question—should the United States continue to depend on countries with relatively low medical standards to man our hospitals and to provide us with a significant proportion of our general physicians? These relatively undeveloped countries can ill afford to supply physicians to us. Indeed, if we were fulfilling our international responsibilities, we should produce a surplus of doctors beyond our needs to send to underdeveloped countries—as the Russians are already doing.

NOT INTO GENERAL PRACTICE

It is clear why graduates of American medical schools tend not to go into general practice. Since the Flexner report, the medical schools have pursued a policy which favours the education of experts—i.e., scientists and specialists—rather than general physicians. This policy was aided and abetted by:

1. The high priority given by medical-school admission committees to applicants with demonstrated scientific ability.
2. A medical-school curriculum concentrating on minutiæ of preclinical science sometimes at the expense of clinical teaching.
3. The preferential appointment by our great teaching hospitals of interns and residents with scientific ability rather than those with clinical acumen.
4. The appointment of scientists interested in research in one of the preclinical sciences instead of clinicians as heads of clinical departments.
5. The availability of large sums for medical research with a concomitant lack of financial support for medical education.
6. The development of the specialty boards.

And last but not least,

7. The patient's immediate acceptance of and willingness to pay for the services of the specialist.

The policy of producing highly qualified scientists and specialists must continue. It has been responsible for the flowering and the excellent reputation of American medicine. We must be sure that the highly specialised research programme of our medical schools be stimulated and expanded if we are to remain in the vanguard of those contributing to medical advance. Students now being educated in ever-narrowing fields will not only contribute to research—they will also use their highly specialised knowledge and techniques for the patient's benefit.

But, at the same time, this policy has created new and serious gaps in general medical care. The educational needs of the specialist and scientist on the one hand and general physicians on the other grow farther and farther apart, and it is increasingly difficult to include them within the compass of the medical curriculum. The low-ranking student who cannot make the grade in our research-oriented curriculum drifts off into general practice. This raises a most serious question. How can the medical schools continue to provide top medical scientists and at the same time graduate competent physicians in numbers adequate to meet our medical care needs?

THE PRESENT UNWISE COMPROMISES

When we examine the situation closely, we realise that the compromise reached by our present medical curriculum does an injustice both to the education of the expert as well as to that of the general physician. As has been pointed out in the studies by Helen Gee,[5] the medical student body is a heterogeneous group both in ability and motivation. In our attempts to reach this broad spectrum of students, we have been forced on the one hand to teach the expert at too elementary a level while presenting an overspecialised curriculum to the future general physician. For example, our biochemists have complained that so much time is spent teaching the alphabet of the science (i.e., definitions such as that of hydrogen-ion concentration) to students with a minimal chemical background that relatively little time remains for the teaching of biochemical theory. In our teaching of biostatistics in preventive medicine at the Harvard Medical School, we face a spectrum of students stretching from advanced mathematicians to those who have barely learnt the principles of elementary algebra. We have had to give preliminary instruction to this latter group before beginning the regular course. But, even so, the advanced students are never really challenged. These compromises will continue to impair the future of medical science and of medical care in the United States as long as we depend upon a single medical curriculum to do both jobs.

5. Gee, H. H. Differential Characteristics of Student Bodies in Selection and Educational Differentiation. Report of a conference held May 25–27, 1959, at the University of California; p. 125.

A WAY OUT

A possible way out of this impasse is to follow the lead of schools of technology such as the Massachusetts Institute of Technology. They have recognised that the educational needs of the physicist and the engineer are different. Although students entering these fields may start off together, their curricula diverge. This is not to say that a student selecting one of these may not change to the other if he so decides and if his qualifications permit. Students with a special interest may also select elective courses in the other curriculum.

In medicine a similar programme is possible. Two curricula can be designed—one for research-workers, specialists, and future professors and the other for general physicians. For purposes of discussion and debate, I will give examples of the curricular changes which illustrate the principles which might be followed if a two-curricula system were adopted.

The research specialist curriculum must include more instruction in the newer preclinical sciences and in mathematics. For example, recent developments in physics, electrical engineering, and mathematics open new pathways to important medical knowledge not accessible to conventional research methods. At the present time, most clinical research tends to be limited to the study of first-order reactions—i.e., one-to-one relationships. Now, application of mathematical theory makes it possible to interpret complex interrelated systems such as that of the absorption of fats from the intestine where splitting and recombination of compounds and recirculation take place simultaneously. Or, through multivariant analysis it is now possible to study the function of a complex organ such as the kidney. Also, newer mathematical models of physiological functions such as that of muscular contraction now provide better hypotheses for the inductive scientist to test in his experiments. In biochemical research, mathematical analysis of randomly split peptide fragments now makes possible the determination of the order of aminoacids in a protein, thus shortcutting the painfully slow process of splitting linkages with specific enzymes.

Such newer knowledge will also assist the specialist in his care of patients. For example, analysis of electronic records as has been demonstrated by Pipberger for the electrocardiogram gives promise of relieving cardiologists of the routine reading and the interpretation of tracings. These newer developments in medical research and in specialty practice have been abetted by the continuing development of computation systems and the increasing availability of such equipment.

Therefore, the curriculum for the student looking toward a career in medical research or in specialty practice must include enough mathematics, physics, and electrical engineering to enable him to work effectively in research teams on which PH.D. scientists in these fields will be represented. This is similar to the present need of the clinical investigator for a basic knowledge of biochemistry. Depending upon individual interests, students will have to learn enough mathematics to handle problems concerned with probability theory, must master differential and integral calculus, and in many cases differential equations—enough electrical engineering to use this growing technology in the design of his experiments and enough understanding of physics to incorporate current theory in the study of such phenomena as perception. Time for such study can be made available by shortening of the clinical teaching in specialties not in the field of the student's interest, permitting many more elective courses, and if necessary, lengthening of the curriculum in particular fields. Thus, a student looking forward to a future in research on perception may spend more time in ophthalmology and less in genitourinary diseases, while one interested in the research on the physiology of the kidney might reverse his selections. Certainly, education of the general physician in a different curriculum will add flexibility to the curriculum of the clinical research-worker and the specialist.

The curriculum for the general physician should be shorter than the present one. Condensed medical curricula compressing college and medical school instruction in a six-year course have been proposed by Johns Hopkins University, Northwestern University, and Boston University. It is difficult to see how such a single condensed curriculum can be satisfactory both for the scientist and the general physician when the present longer one is not. But, such a condensed curriculum would lend itself to the education of the general physician at about the level of our present internist. With such a shortened curriculum many more doctors could be educated than under the present system. This assumes, of course, that there also would be a curriculum for the education of the scientist and the specialist.

MORE SELECTIVE EDUCATION

The key to the new curriculum for the general physician is selectivity of those scientific facts and theories germane to his particular task. That task consists of the general supervision of health and medical care, including preventive medicine, the treatment of minor illnesses, the practice of minor surgery and perhaps normal obstetrics, and the screening of patients for early manifestations of severe or chronic illness in which early treatment gives a better prognosis or a more comfortable life.

Much time in the present curriculum is devoted to learning an almost infinite number of details, many of which are not needed by the general physician. For example, during my medical-school education, I was expected to learn the origin and insertion of all of the striated muscles of the body. This was the era of the anatomist—gross, microscopic, or morbid. When his influence declined, with the rise of biochemistry, this anatomical requirement was deleted from the medical curriculum. But, instead, students are expected to learn, in the same unselective way, the names and functions of all the enzymes in all the known chemical reactions in the muscles of the body. To be sure, knowledge of the principles of enzyme action and of the Krebs cycle is important and should be taught to the general physician. But, the details of the individual chemical reactions, of great interest to the biochemist and the expert in metabolism, do not concern him.

Just as research has become more complex, so has medical care. The evolution of the specialist in medicine, the increasing use of clinical and other laboratories, and the many paramedical assistants all demand a general physician who knows how to interrelate all of these essential services for the benefit of a particular patient. Moreover, the increasing burden of chronic disease associated with lengthening life-expectancy demands more detailed supervision of the individual patient. This is so whether the patient is cared for by the specialist services of the hospital or at home with the assistance of community health services. The curriculum of the general physician, therefore, must include time for the detailed supervision of, for example, the ambulatory cancer patient whose treatment may require at particular times a surgeon, a radiologist, or radiotherapist, a specialist in metabolism, an anæsthesiologist to control his pain, the psychiatrist, selected laboratory tests, or the services of a public-health nurse, medical social worker, dietitian, or physiotherapist.

Most important of all, the general physician must have had special teaching on the theory and technique of screening patients for early manifestations of those serious or chronic illnesses which are better treated early. Under his general supervision, he must be able to refer patients, so identified, to proper treatment even though it require a particular specialist, an unusual laboratory test, or a service to be given by a member of one of the paramedical professions. This means that the clinical competence of the general physician must be excellent. The curriculum must stress clinical instruction particularly on patients in the early stages of illness.

These are representative examples of the kind of curricular changes that would be possible if the two-curricula system were adopted. Depending upon his special field of medical education the teacher can visualise the changes which would improve his teaching programme if the additional flexibility of a two-curricula system were made available.

If a two-curricula system were adopted, there would be another advantage. The medical schools could have a more selective admission policy. Candidates for admission to the research-specialist curriculum would be expected to have different qualifications from those applying for the general-physician curriculum. The former should attract the kind of student who has been turning away from medicine towards a career in mathematics or in such sciences as physics and chemistry.

In contrast, the general physician's curriculum should attract some of those dedicated and able students who have hesitated to apply or have been frightened away from medical school because of their inability to compete at an advanced level with those more gifted in the sciences. It would be a great novelty to see the top man in a medical-school class yearning to be the best physician rather than the best scientist.

COSTS OF GAINS

Increased recruitment will have to be supported by extension to medicine of such scholarship aid programmes as the pre-doctoral fellowship programmes of the Federal Government. Large sums for building and the operation of medical schools will also be needed. It should be pointed out, however, that there is no reason why this

particular plan should cost more than other plans for expansion of medical schools. Indeed, by shortening the education curriculum for general physicians, it should cost less.

Recruitment of faculty for this proposed programme should be less difficult than recruitment for a mere expansion of the present medical schools. As in the latter case, more scientists will have to be recruited for preclinical teaching. However, for clinical teaching an unused resource could be tapped. Many skilful young clinicians in our teaching hospitals now have no academic future because they are not adept at laboratory research. Many are now forced unwillingly into private practice. They would make excellent full-time clinical professors, many of whom will be needed if we develop a curriculum directed toward the education of the general physician.

TWO CURRICULA BUT ONE SCHOOL

One point must be clear. My suggestion for reorganising medical education provides for two curricula in the same medical school and not for different curricula in separate schools. This latter system, which I oppose, would have two major defects. It would educate medical scientists in an environment where there would be insufficient exposure to the problems of clinical medicine demanding thoroughgoing research. But, more important, it would result in vocational schools for general physicians. As in the case of the present education of the internist, the curriculum for the general physician must be soundly based on medical science in a school where the student is in close contact not only with clinical teachers but also with research-workers and specialists. To do otherwise would bring a rapid return of all of the evils of the pre-Flexner era.

This proposed reorganisation, if adopted, would have to be followed by a rearrangement of the structure of our teaching hospitals. The graduates of the scientist-specialist curriculum would be given appropriate appointments on the specialised services of the teaching hospitals. After a year on the general medical or surgical services, they would begin to concentrate their time on a field of interest. In contrast, the general physician would be appointed to a rotating service with most time spent on the general medical service. Special arrangements for experience in minor surgery, normal obstetrics and outpatient medicine would be made. Patients using the hospital almost exclusively for their medical care in the emergency service, the outpatient department, and on the wards would be assigned to a general physician in training who would supervise the continuity of care.

When his period of formal education is completed, the general physician must continue in his practice to be closely related to the scientist and the specialist, and the hospital. Individual physicians cannot practise good medicine when they are isolated from specialists and from hospitals. Whatever the system of education, group practice units comprising all of the specialties and using personal physicians specially educated for this responsible task could provide continuous health supervision and timely and appropriate medical care of a quality which is not generally available at the present time. Indeed, it is my considered opinion that such continuous association of general physician and specialists is much more important for the maintenance of high quality in the general practice of medicine than is the presence of esoteric minutiæ of preclinical science in the curriculum of the medical student.

CHOICES

Our medical schools must decide whether they will meet the responsibility of providing an adequate number of general physicians to meet the medical care needs of the American people. The situation is already critical with overworked internists and general practitioners unable to satisfy the urban need, with an absence of physician's services in many rural areas, and without enough medical graduates to fill internships and residencies even in hospitals with excellent postgraduate programmes.

A two-curricula plan has been presented and could solve the problem. But, if the medical schools really decide to meet this responsibility, they also have other choices. Some educators believe that the present system would be adequate if properly implemented. In contrast, others believe that with our highly developed system of specialist medical care and with the support of the many paramedical professions, personal health services can be delegated to specially educated public health nurses or to individuals educated in a modification of the Russian feldsher system. I do not share these views. I believe that the American people want personal health services from a physician educated specifically for this important professional responsibility.

But in any case, medical educators must not let the issue be settled by default. It is not enough to point with pride at the excellent medical care provided within the ivory towers of our great teaching hospitals or to the relatively few excellent internists who leave such centres to go into practice. Such centres set a high standard for the care of our very sick patients in hospital. But, quantitatively they meet but a tiny part of the medical care needs of the people. Much more important, as the gaps in medical care widen, they are being filled by relatively poorly educated foreign physicians and by such cultists as chiropractors and naturopaths. The problem is urgent and the question raised is not whether we should adopt a two-curricula system but how our medical schools can best meet the challenge of providing personal health services to all Americans.

SUMMARY

A plan is suggested which could (1) strengthen our medical research programme, (2) improve the quality of our medical specialists, and (3) provide the number and kind of physicians needed for the medical care of the people of the United States.

Medicine and the Law

Death following Disconnection of a Respirator

AT an inquest in Oxford on Feb. 22, a jury returned a verdict of accidental death in the case of a 16-year-old boy who had been treated for tetanus, and added that a contributory cause was the accidental disconnection of the tracheostomy tube from a mechanical respirator.[1]

Medical evidence was given that a tracheostomy had been undertaken. Next day the patient's condition had worsened. Curare was administered, and artificial respiration was applied by a mechanical respirator. In the early hours of Feb. 1 the machine became disconnected from the tracheostomy tube. When the heart was found to have stopped, it was massaged and restarted; but the patient died twelve hours later. A nurse said in evidence that she left the patient for no more than three minutes, to collect his food from the kitchen; another nurse was close by.

1. *Birmingham Post*, Feb. 23, 1961.

Conferences

PROSPECTS IN HEALTH EDUCATION

FROM A CORRESPONDENT

A CONFERENCE for medical officers of health, organised by the Central Council for Health Education, was held in London on Feb. 21–24.

The Future of Public Health

Dr. I. A. G. MACQUEEN taxed his colleagues roundly with failure to use new methods and new thinking in meeting modern health challenges. In 1930 the need had been for environmental hygiene, infectious-disease control, and attention to the physical health of mother, baby, and schoolchild, the health department being essentially medical. With these tasks declining rapidly, we had not, in 1960, adapted health departments to the problems of this decade—notably, to accidents of all kinds, health education, the prevention of maladjustment and delinquency, rehabilitation of the handicapped, and the welfare of the elderly. Home accidents killed more people than poliomyelitis or tuberculosis at their peak ever did, and there was wide agreement that the roots of mental disturance and delinquency lay in the pre-school years. These tasks were too important to leave, and if the health department did not meet these responsibilities other bodies would, and there was the real possibility that staff and functions would pass from health departments to others. Dr. MacQueen wanted to meet these challenges by substituting a team-work "democratic" approach for the past autocratic one, and by expanding the duties of the health visitors or public-health nurses, who should be more numerous and better paid. Health and welfare departments should be amalgamated forthwith, and medical officers of health should turn their attention to new fields of research—e.g., the epidemiology of disease in the declining years. This stimulating point of view evoked much sympathetic discussion subsequently, and it was noted that public health is still very badly taught, especially in London.

What the Public Thinks

As chairman of the recent B.M.A. committee on the future of broadcasting, Dr. H. D. CHALKE launched a not unexpected attack on commercial advertising, especially on television. These techniques were devilishly effective, and we should claim a much bigger purse to use television, strip cartoons, and so on for health purposes—to dispel, for example, such ignorance as was shown by the 28% of the population who believed tuberculosis to be non-infective. His studies in Camberwell—in which medical students' help had been invaluable—showed too that only 1 mother in 6 or 7 knew what vaccination meant. Dr. Chalke had then found out by questionary what forms of publicity reach the public: among 600–700 replies, mostly from higher-income groups, television emerged well ahead of all others, though radio and newspapers were rated high by adults. Pamphlets and posters were rated so low that they had been eliminated from his clinics (but by no means everyone at the meeting agreed with this assessment): if used, posters round the wall should repeat one simple message, then all be changed after a week to a new one. In discussion the suggestions were made that insurance companies be asked to subsidise health education and accident prevention, and that council rent collectors or those surveying property might help with questionaries: each area differed and comparisons of attitudes might be fruitful.

Medicine on Television

Dr. RICHARD FOX spoke of the complexities and problems of medical programme production, which required the closest cooperation between a lay producer who understood science and a medical man who knew something of journalism. Ethical problems loomed large but they were not new: the size of the audience and clarity of the image merely brought the issues into sharper focus. While any medical publicity or education interfered to some extent in the relations between a doctor and his patients, 85% of over 100 general practitioners had thought such interference beneficial and only 8% had been against televising medical topics. This accorded well with current B.M.A. policy, which had emerged from its apparent ambiguity of recent months and was now keen on health education by this means. Television was so powerful that doctors in popular series, be they never so anonymous, could become national figures, with names and photographs in the press. Such publicity, useful though it might be to the public image of the profession, might be expected to fill the consulting-room, and for this reason Dr. Fox suggested that performers should be chosen from academic or local-authority fields, or, failing that, from those who were whole-time in the N.H.S. Though television had been shown to change attitudes, he was less certain how far it influenced behaviour: after a recent propaganda programme on immunisation, for example, the numbers coming forward had *dropped*. (Dr. CHALKE, on the other hand, said he had done a normal year's immunisation in a day or two after his 6 o'clock news appeal regarding diphtheria in Camberwell.) Finally, Dr. Fox called for a more aggressive approach by the B.B.C.—it was the only mass medium free of pressure groups and advertising revenue—to the commercialisation and debasement of moral and æsthetic tastes perpetrated daily on the other channel.

Mr. JAMES MCCLOY, a B.B.C. producer who was also a biologist, said that medical programmes were very popular and could expect regular audiences of 5–10 million: medicine, in fact, did well in the fight for restricted programme time, and doctors, he had found from long experience, came off better on television than those from any other non-acting profession. Programmes were put across in three ways—as dramatised documentary, as a reconstruction on film with real people (*On Call to a Nation*), or studio-built (*Matters of Medicine*). Mr. McCloy believed it best to use "real" doctors in an intimate approach and to eschew all deception: he tried to bring the television set "into the circle round the hearth" rather than to erect a proscenium arch between the viewer and the "performer". (Wide appreciation was expressed in the conference, however, for *Emergency—Ward 10*, and the issue of "real" versus "dramatised" medical propaganda split the conference.) Straight health talk Mr. McCloy believed less effective than the indirect approach. The B.B.C. audience-research department's surveys had failed to show adverse effects: any change in emotional level, even after surgical scenes, had been towards lessening of anxiety and hypochondria, and increasing confidence in the general practitioner.

Describing his brief appearances on the medium, Dr. I. A. MACDOUGALL had kind words to say about his experience with the B.B.C. The producer had been most courteous and had let him handle the material as he thought fit. But the I.T.A., over a discussion on cancer and cigarettes, had demanded a flippant approach and prevented him from putting his case as he wished to. Dr. C. S. NICOL had also met many problems with lay producers and scriptwriters over the I.T.A. programme on venereal disease. There had been months of battle "to get things right" and Dr. Nicol said that any future "expert" must prepare himself for this. The programme had been praised in the *British Medical Journal* and had flooded V.D. clinics throughout the land, though only 20% of these new cases were found to have the disease: at St. Thomas's the attendance rose from 90 to 150 per week. It had been an invaluable opportunity to bring present dangers before the public, and one for which they had long campaigned.

How to Handle Journalists

Medical officers of health, said Dr. HARVEY FLACK, editor of *Family Doctor*, should make the best possible use of local publications, be ready to advise on the subediting of medical matters, give interviews on current topics, and send out advance copies of their annual reports with the items of particular importance written simply and clearly indicated. It must be made plain that anything said to a journalist was legitimately taken down and might be printed—even if said over the telephone—but where it was made clear what is "off the

record" and what was for publication, Dr. Flack, in 25 years' journalism, had never known the confidence broken. An editor, furthermore, would, if asked, always have the material read out over the telephone before publication. Documents released to the Press should have the dateline clearly shown and it should be appropriate to the printing problems of the chosen papers. Medical writing for the lay press required practice, for medical training promoted jargon. *Family Doctor*, he was glad to say, had a circulation of over 100,000 and had made a profit for some years. It, and the pamphlets and books, made a big contribution to health education. Both it and the Central Council for Health Education were pleased to print propaganda pamphlets very cheaply—but only in very large numbers. Dr. Flack counselled against itinerant advertisers who offered to print such pamphlets free, using local revenue from advertising. Such attempts to use the medical officer of health and his local authority to make money could only bring both into disrepute. Doctors should also beware the public-relations "ghost" writer who would take some published comment, "angle" it to serve a commercial end, and seek permission to print under the doctor's name.

* * *

It was good to find a large group of medical officers of health stimulated by present challenges and anxious to do more than "chasing decimal points down the vital statistics of our over-fed country"[1] as a writer in *The Widdicombe File* put it when he criticised the tendency of preventive medicine to bask in the glory of past triumphs. The challenge of preventive psychiatry was much to the fore, and experiments could start soon—early attempts must be on an experimental footing, for little is known of this approach, and that little is so far discouraging.[2] It was very encouraging, however, to learn that some medical officers of health propose to use mental-hospital staff rather than appoint new local-authority psychiatrists, and their repeated requests for closer local-authority/mental-hospital liaison should be emphasised again and again. On this showing, the medical officer of health may win the new and illustrious future that his social importance clearly merits.

Public Health

Mass Radiography in Scotland

1,844,268 people participated in a mass radiography campaign in parts of Scotland in 1957–58.[3] This represented 68% of the total adult population of these areas. In Edinburgh, Glasgow, Aberdeen, and Dundee the response-rate was as high as 76%. This excellent result was largely due to effective publicity.

12,094 new cases of tuberculosis were found, 4328 being regarded as active cases (2·35 per 1000), the remainder (7766, 4·26 per 1000) having tuberculosis requiring observation. Other conditions detected included bronchiectasis and emphysematous disorders (4956), cardiac abnormalities (4338), pneumonoconiosis (2529), and malignant tumours (746).

Two-thirds of the cases of tuberculosis were found in Glasgow and four-fifths of the total in the four cities. Most of the active cases were found in younger women and older men. Nearly two-thirds of the active cases were in men.

A supplementary survey carried out in Edinburgh on those who did not cooperate in the original survey suggested that the prevalence of the disease may be higher among those not presenting themselves for examination. The considerable cost and effort involved in the supplementary survey was, however, not commensurate with the results achieved.

1. *Lancet*, 1956, ii, 939.
2. McCord, W., McCord, J. Origins of Crime, New York, 1959.
3. The Two-year Mass Radiography Campaign in Scotland, 1957–1958. H.M. Stationery Office, 1961. Pp. 98. 7*s*.

In England Now

A Running Commentary by Peripatetic Correspondents

NOTHING is more fascinating to us non-combatants, clutching our Saturday sixpences in our hot little hands, than the spectacle of financial moguls clobbering each other à outrance with bags of bullion. Living only for their work, to judge by their expense accounts, these warriors are a harassed and battle-weary bunch, with one eye on Mr. Clore and the other on the Director of Public Prosecutions, while the Inland Revenue's hatchet-men breathe heavily down the backs of their necks. Never are they sure whether that sharp pain in the wallet area is due to the impact of a take-over bid, or is caused by one of the emboli which T.V. assures them are hurtling along their arteries like tube-trains in the rush hour. And now they, or anyway their ambitious understudies, are bedevilled by two sinister and omnipotent characters known only as "Roscoe" and "J.B.", whose assignment is to eat with them in public and entrap them into vinous and gastronomic gaffes.

Chain-smoking so furiously that I could hear the tobacco-tar hissing as it dripped into his gastric ulcer, one Would-be Director wept as he told me that whatever he ate in restaurants, be it a simple *langouste de Méditerranée au Thermidor* (because the baked beans were off) or spam and salad, he always found himself drinking Liebfraumilch B--e N-n, and it gave him the waterbrash something terrible . . .

In contrast, one of his colleagues has nightmares in which Roscoe having demanded a boiled egg and old J.B. (nothing but the best for old J.B.) *ortolans au Roi Frédéric IX*, the wine-waiter announces, "No B--e N-n in the joint, Mac., better make it three caffs." One has the impression that the Grey Eminence J.B. and the omniverous Roscoe are foreign agents seeking to undermine the confidence of British finance. If so, the Institute of Would-be Directors could now strike back by engaging a Young Doctor to sit in on all business lunches where these two are in action.

Then when Roscoe clamours for *sole paupiettes* and J.B., the awkward old so-and-so, rissoles (and let's see him pick a wine to suit *that* lot) the Young Doctor would announce that rissoles, on top of smoked salmon or whatever else old J.B. had been previously doing his gastric mucosa no good with, would send his blood-cholesterol up so high it could run a diesel. . . . At this point the Would-be Director takes the trick by ordering a pot of tea for four and a plate of sicklies, thereby emerging from the contretemps with diminished blood-pressure and heightened reputation.

* * *

We had just completed examining the last candidates and a quick assessment of the results suggested a very small pass-list. However, a great many candidates were borderline and a review of their papers was obviously indicated. A motion to delay further consideration until *post cibum* was carried *nem. con.* and the examiners adjourned to a neighbouring establishment for appropriate restoration of metabolic reserves. My colleagues all supplemented their diet with moderate amounts of a liquid capable of yielding calories on oxidation as well as producing certain additional interesting effects; being teetotal I preferred to take a liquid with only solvent properties.

When we began rescrutiny of the examination results several candidates' papers were now judged to be rather better than our earlier assessment had indicated and the marks could justifiably be adjusted to permit a pass. In one case, however, I disagreed with my colleagues' desire to raise the marks enough to turn the scale until one of them in exasperation explained my stubbornness by the remark: "It's that —— water you drink!" The candidate got his pass, but he certainly does not know of the metabolic mechanism which led to it.

Question for study: What steps may be taken to ensure that examiners receive proper preparation for their examinations?

* * *

Mr. Todd's views on the ætiology of lung cancer remind me of our Mr. Snip's observations on the treatment of premature baldness.

Singeing, he informed me, is the only treatment of value. When I expressed my doubts he proceeded to explain the rationale of the treatment. "As you know Sir, each 'air is 'ollow Sir. When you singe the 'air Sir, the 'eat of the flame burns off the top of the 'air Sir and the smoke goes down the 'ollow 'air Sir and stimulates the roots Sir. Then the 'eat seals off the top of the 'air Sir and there you 'ave a 'ollow 'air Sir, full of smoke, stimulating the roots Sir."

I gave in quietly.

* * *

I've just bought one of those plastic men for my first-aid class. INCREDIBLE! it says on the box, and certainly there's something macabre about assembling the skeleton from the same kind of instructions as the kids' little plastic planes. "Place stud on Right Hand in T-shaped pocket in lower end of Forearm"—too easy, really, I thought, till I found I'd got the hand the wrong way round. "Surely the thumb should be the same side as the radius?" my wife burst the bubble of self-esteem.

Ah, well. Tomorrow I'm going to tackle the little bag marked "All the Vital Organs". I ought to be able to get *them* right. But should I paint them the bilious greens and yellows favoured by Jamieson, or will that offend our squeamish lady members? Perhaps a delicate mauve would be better.

* * *

A PETITION

Dear Gentlemen,
Do read this plea.
It doesn't come from only me—
(A big broad chap and extra tall)
But I should say, from nearly all
The millions who have sweated there
In your abode at 8, Queen Square.
We learn Life's ways aren't decked with flowers,
In this imperfect world of ours—
Exams are times of strain—not bliss,
But must we really suffer this?

In basements low, they have to keep
Their flocks of frightened, jostling sheep,
"Is this my foot?"—or—"That your leg?"
Ten coats fall off one plaintive peg!
(And oh, Sirs, heed. Before, too late,
Some frail and gentle candidate
Anguished in "stress", gives up his ghost
As sacrifice, for all the host
Of those who wonder what to do
When "you know where's" are far too few.)

And then—at last, the moment comes!
With twiddled nails and bitten thumbs,
Our flocks are freed, we storm the stairs—
Man's Dignity? "Baa-baa," *Who* cares?
I've been through all this game before
And so I know the sloping floor
On which my creaking desk can tilt—
And oh, the way that thing is built!
The paper, off the small top, slides—
My knees fight with its flimsy sides—

I wind my legs around in vain,
And then unwind them back again—
While bodies come and bodies go
And stub my large and anxious toe.
Forgive me if I'm in the wrong,
The time is short, the questions long.
With numbing knees and aching seat,
I beg you, Sirs, to hear my bleat—
(One stamp enclosed) Please answer me,
"IS THIS THE WAY IT HAS TO BE?"

Letters to the Editor

THIACETAZONE AND ISONIAZID

SIR,—In your leading article (Feb. 11) you mention that clinical trials of chemotherapy in tuberculosis which require large numbers of patients could probably only be carried out by an international body, such as the International Union against Tuberculosis.

The Union has, in fact, just begun an international prospective chemotherapy investigation that is expected to cover 700 patients from 30 tuberculosis hospitals and sanatoria in more than 20 countries. Cultures of tubercle bacilli will be sent for sensitivity testing to 5 reference laboratories in Europe; and the whole investigation will be coordinated from London. The patients will be treated with a uniform chemotherapeutic regimen of streptomycin, *p*-aminosalicylic acid (P.A.S.), and isoniazid for 28 weeks, followed by a further period of treatment with P.A.S. and isoniazid. The primary object of the investigation is to study the causes of failure of chemotherapy; and with such a highly effective drug combination, large numbers of patients will be required.

The committees on chemotherapy and laboratory methods, whose presidents (Prof. J. W. Crofton and Dr. N. Rist) initiated the investigation, are to carry it out. The committees recently approved a modification of the treatment protocol. If this is accepted by the cooperating centres, it will allow the efficacy of the standard 3- and 2-drug regimens to be compared with a regimen of 3 drugs initially, followed by isoniazid alone, which you mention in the leading article. Patients who fulfil certain stringent bacteriological criteria of sputum negativity after 28 weeks' standard treatment would be placed by random allocation into 2 groups, 1 to continue on P.A.S. and isoniazid, the other to have isoniazid alone. The information obtained could be of considerable value to the less favoured countries, where the cost of drugs and scarcity of hospital beds preclude effective and large-scale combined drug treament.

This is the first attempt by any organisation to carry out a prospective cooperative chemotherapy investigation internationally on a large scale; and there will be many difficulties. But if it succeeds and in addition it is possible to include a controlled comparison with random allocation to treatment groups, the International Union against Tuberculosis will have shown the way in an almost completely unexplored field of international cooperation in medicine.

GEORGES CANETTI
International Union against Tuberculosis, Pasteur Institute, Paris, 15. Associate Coordinator of the Scientific Commissions.

CARE OF THE INJURED

SIR,—I am sure that many surgeons would support Sir Alexander Drummond's view (recorded in your annotation of Feb. 18) of the great value of smaller hospitals in the treatment of accident cases. The majority of such patients need simple urgent surgery and this can be provided only by a large number of operating teams. Air-raid and battle casualty experience has shown that, taking all types of case, on the average one operating-theatre and team can cope with one patient per hour. Even the largest accident hospital will be limited therefore by the number of its operating units, and with a big influx of cases there will be quite a number who have to wait for hours for operation. This happened in the last war and in one famous raid many patients waited for days in one hospital for operation while surrounding hospitals were empty. In contrast was the brilliant urgent surgery of the battlefield provided by the little units—the field surgical units—surely one of the triumphs of war surgery which amply demonstrated the value of multiple small operating units.

There are many other arguments for dispersal of cases, such as the dangerous waste of time in transport to a central unit; fatigue of staff with a mass of cases; the dangers of complete disorganisation of a large single unit by failure of an essential service; and the provision of adequate staff in a big unit. It is only in recent weeks that the Birmingham Accident Hospital announced that they could not provide a 24-hour accident service because of a 50% shortage of radiographers. Many such difficulties are far less serious if they affect only one or two smaller units.

If the accident services must be organised, let the Clores and the Cottons of Accident Surgery remember that, however large the hospital, there is room for only one patient at a time in one operating-theatre; let them advise the smaller hospitals if they must but not "take them over"; let them organise on the basis of multiple chain-stores and not of emporia.

London, W.1. GEORGE QVIST.

THE DOCTOR'S PLACE IN THE PATIENTS' HOSPITAL

SIR,—I write from the Child Guidance Service to give a very warm welcome to Dr. Hayward's article of Feb. 18. I hope your readers will have appreciated that far from being a specialised article for mental-hospital psychiatrists, it contains matter of great importance for every doctor in clinical practice.

In the last section of his article, that dealing with the mental hospital and the community, Dr. Hayward warns us of the serious situation that great numbers of chronically ill patients may now be discharged from mental hospitals "to the care or neglect of the community". It may well turn out that excellent provision is being made by local health authorities for these people, in the way of day hospitals, occupational centres, increased establishments of mental welfare officers, and the like. But whether or not these plans prove sufficient and successful, they cannot have more than a superficial bearing on that fundamental unit of community life, the family.

It seems to me a very odd fact that, while all of us as individuals are (or have been) members of a family, the only medical people who appear to appreciate the year-in and year-out realities of family life as such are general practitioners, local-authority medical officers, and psychiatrists in child-guidance clinics. Yet it is impossible to begin to understand, and therefore substantially to help, any person without taking into account not merely his "social background", but the nature of his closest personal relationships. This means the family. Further, the more dependent a person is on others, the more important in practice is this consideration. Therefore the need to consider family ties applies particularly to children, to old people, and to invalids, whether physically or mentally ill.

The burden which will arise if our mental hospitals are to be designated obsolete will be borne in truth by the family. The community's burden in making provision for amenities of various kinds cannot be compared in any way to the tremendous private and personal burden of, say, the wife and mother whose schizophrenic husband is at home. Advances in psychiatric treatment render many such patients "recovered" in the social and occupational sense, but recovery in terms of the warmth of living personal relationships is a different, deeper, and more subtle matter. And the ultimate effect on a child of a parent at home who is emotionally blunted, even if no more disturbing symptoms are present, may be far more damaging than, say, the human irritabilities, inconsistencies, and stupidities of parents who are not mentally ill. For many children, especially younger ones, I would even judge the absence of parents to be less disastrous than this experience.

In as far as this kind of consequence has been envisaged by the planners, the difficulty is supposed to be met by the suggestion that psychiatric social workers would be able to deal with these family problems on a domiciliary basis. Psychiatric social workers can, of course, give an enormous amount of help with their patience and skilled understanding; but they would be the last people to claim some magical ability to remove the stresses arising from an incurable personal situation.

The following example illustrates the kind of situation which will become more frequent. It is perhaps more dramatic than most, but no more serious. A chronic schizophrenic mother experienced paranoid delusions on behalf of her adolescent daughter, supposing people to be persecuting the child. It followed that the child did not attend school for several months, being kept virtually isolated in the company of her mad mother. The end-result of the difficulty was that the child was removed by a court order to a children's home, obtaining thereby the advantages of education and social contacts, but deprived of home life; while at home her kindly father remained in a state of perpetual anxiety, and her grown-up brother was said to be a morose and unsatisfactory character. . . . Could anyone claim this solution to be either humane, enlightened, economic, or even sane?

I entirely agree with Dr. Hayward's suggestion that we are in danger of dealing with the problem of chronic mental illness by denying its very existence. If this trend is allowed to develop unchecked, we will be compelled to discover the hard way that such a denial cannot be maintained indefinitely. The secondary increase in breakdowns of many kinds will become apparent; children's officers, probation officers, and child-guidance teams will be more overworked than ever; and is it even possible that the admission-rate to mental hospitals will rise again? Let us hope that there will be sufficient beds left standing.

Child Guidance Clinic, Chislehurst, Kent. JUDITH WATERLOW Medical Director.

ORIGINS OF CRIME

SIR,—It is with some reticence that I offer a comment on your annotation of Jan. 7, since I have had little more than the ordinary medical experience with juvenile delinquency. However, the statements, "Of all the influences studied, the mothers' personalities seem to be the most significant in the genesis of criminality" and "Paternal absence, cruelty, or neglect tended to produce criminality in the majority of boys", may unfairly place a heavy burden of guilt on parents already driven to distraction by their delinquent children. I suggest there may be a logical fallacy involved. The demonstration that parents whose behaviour is socially defective have children whose behaviour is socially defective surely does not necessarily mean that there is a simple, direct causal relation between these two phenomena, as these two statements imply. One alternative explanation is that both derive from a common source—for example, a hereditary defect.

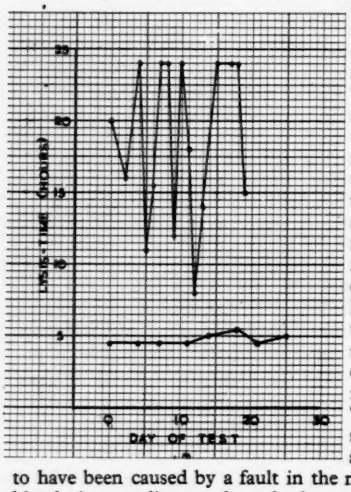
Having been exposed in recent weeks to the self-recriminatory anguish of several parents of delinquent children, I feel that it would be humane, as well as scientifically correct, to explore the validity of each of the whole group of hypotheses which may explain the association of delinquent parents with delinquent children.

Ochsner Clinic, New Orleans, Louisiana. WILLIAM LOCKE.

BLOOD FIBRINOLYTIC ACTIVITY IN WHITE AND BANTU SUBJECTS

SIR,—Unless I misunderstand their letter, Mr. Antonis and Dr. Bersohn (Feb. 18) have measured blood fibrinolytic activity by two methods, that of Bidwell [1] and that of Fearnley et al.,[2] and found little variation in individuals tested on successive days, but considerable variation in some, though not in most, of their volunteers when the interval between the tests was several weeks. They conclude surprisingly that either the method or the way in which blood is obtained is responsible.

A more fitting explanation of these findings is that blood fibrinolytic activity varies considerably in some people; and all our experience points to this. The accompanying figure illustrates what might be termed the extreme of behaviour of blood fibrinolytic activity. The upper plot is from an atherosclerotic woman inpatient in the fasting state from whom blood was obtained at 8–8.30 A.M., and the lower plot is from a nursing sister from whom blood was obtained at 5–6 P.M. Readings were not taken beyond 24 hours, so that clot-lysis times of greater duration are recorded as 24 hours. The swings of activity shown by the patient are exceedingly unlikely to have been caused by a fault in the method or in obtaining blood, since readings made on 2 other patients on the same days and at the same time did not show the same fluctuations. I believe such variability, which incidentally is not confined to those with manifest atherosclerosis, to be of interest and probably of importance; but it does vitiate conclusions drawn by comparing single readings in individuals; and here I am in complete agreement with Mr. Antonis and Dr. Bersohn.



I cannot agree, however, with their apparent assumption that blood fibrinolytic activity ought to remain constant in the individual, and that if it does not do so the technique of measurement must be faulty. This is analogous to condemning a method of blood-glucose determination, applied without a knowledge of carbohydrate metabolism, because some individuals' blood-sugar levels vary on different occasions. Our ignorance of the control of blood fibrinolytic activity is too profound to permit any such assumption, and the effect of physical exercise [3 4] and diurnal variability,[2 5] and the probable effects of alimentary lipæmia [6] and beer-drinking,[7] suggest that the analogy with the blood-glucose level is not far-fetched. It is only too likely that the level of blood fibrinolytic activity is governed by influences of which nothing is yet known. Certainly we have obtained sufficient evidence that under apparently standard conditions blood-clot-lysis times are relatively constant in some people, fluctuate moderately in others, and grossly in yet others. Natural variability is, I suggest, the reason for Mr. Antonis and Dr. Bersohn's results rather than crude methodology.

This is not to deny that clumsy venepuncture affects blood fibrinolytic activity; it can, and a tourniquet certainly does.[8] The method we use has two disadvantages. When lysis time is long, the end-point becomes indefinite; and an excess of thrombin (over 20 units) in the test undoubtedly hastens lysis time, as pointed out by Dr. Innes [9] of the Birmingham Accident Hospital. We believe we have overcome the former difficulty by a modification of the method,[10] and the latter can be avoided by using not more than 5 units of thrombin in the test.

Gloucestershire Royal Hospital, Gloucester. G. R. FEARNLEY.

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2. Fearnley, G. R., Balmforth, G. V., Fearnley, E. *Clin. Sci.* 1957, **16**, 645.
3. Biggs, R., Macfarlane, R. G., Pilling, J. *Lancet*, 1947, i, 402.
4. Fearnley, G. R., Lackner, R. *Brit. J. Hæmat.* 1955, **1**, 189.
5. Buckell, M., Elliott, F. A. *Lancet*, 1959, i, 660.
6. Grieg, H. B. W. *ibid.* 1956, ii, 16.
7. Fearnley, G. R., Ferguson, J., Chakrabarti, R., Vincent, C. T. *ibid.* 1960, i, 184.
8. Clarke, R. L., Orandi, A., Cliffton, E. E. *Angiology*, 1960, **11**, 367.

DUPUYTREN'S CONTRACTURE AND IDIOPATHIC RETROPERITONEAL FIBROSIS

SIR,—Your annotation (Jan. 14) on the part played by local injury in the ætiology of Dupuytren's contracture, and Dr. Forgan's letter (Feb. 4), in which he mentions Peyronie's disease, bring up the general question of the ætiology of other puzzling fibrosing conditions which occur at characteristic local sites.

I was not aware of Dr. Larsen's work on Dupuytren's contracture and his finding that deposits of hæmosiderin granules can often be seen in this lesion. A few years ago I reported [11] similarly finding hæmosiderin in the fibrous plaque of a case of idiopathic retroperitoneal fibrosis which came to necropsy. I concluded then that trauma perhaps had played the same sort of part as you and Dr. Larsen envisage it doing in at least some cases of Dupuytren's contracture.

Injury is a refreshingly simple cause for an "idiopathic" disease in these days of somatic mutation, autoimmunity, orphan viruses, and wrong numbers of chromosomes.

Institute of Medical and Veterinary Science, Adelaide, South Australia. EARLE HACKETT.

SKELETAL FLUOROSIS

SIR,—In answer to Dr. Wynne Griffith (Feb. 25), may I make the following comments?

(1) Prof. Amarjit Singh and his colleagues (Jan. 28) make a point of drawing attention to the interesting fact that 25% of their cases of skeletal fluorosis did not show signs of dental fluorosis. Presumably such a specific statement would not have been made if the persons concerned had resided outside the heavily fluoridated areas during the early years of life. It is quite unscientific for Dr. Griffith to infer that my conclusion (Feb. 18) is wrong unless he knows the true facts. The same argument applies to the 10% of the population who did *not* exhibit fluorosis.

(2) Dr. Griffith goes on to say that the absence of dental fluorosis in some of these cases is quite irrelevant. But it is well known that although adults may not develop the condition they can show serious signs of fluoride intoxication. As Dr. Dobbs [12] has pointed out, "the absence of signs which cannot be expected to occur is a poor basis for assuming safety."

(3) Sir J. Simon [13] said "we cannot expect to find the effects of impure water always sudden and violent, its results are indeed often gradual and many elude ordinary observation, yet be not the less real and appreciable by a close inquiry." The fact is that as far as the fluoridation of water for general consumption is concerned there has been no adequate scientific inquiry which proves that such a measure is either desirable or safe. John Wesley wrote in 1747 [14] "water is the wholesomest of all drinks." If the medical profession is to safeguard the nation's health let us keep it so.

Institute of Pathology, The Royal Infirmary, Cardiff. R. A. HOLMAN.

9. Innes, D. Personal communication, 1960.
10. Chakrabarti, R., Fearnley, G. R. To be published.
11. Hackett, E. *Brit. J. Surg.* 1958, **46**, 3.
12. Dobbs, C. G. *Brit. dent. J.* 1957, **103**, 267.
13. Simon, J. *in* Manual of Practical Hygiene (edited by E. A. Parkes) p. 58. London, 1891.
14. Wesley, J. *in* Primitive Physick; p. 8. Bristol, 1747.

REPRINTS

SIR,—Dr. Faulds, in his letter of Feb. 11, asks for guidance in dealing with printed cards requesting reprints.

These cards are symptoms, not of bad manners, but of the necessities of the age. A huge populace of scientists, faced with a proliferation of journals, still find only 24 hours in each day; they appreciate a reprint for contemplative reading as keenly as did the limited circle of scholars in the nineteenth century. The printed card is a technical convenience, and I can see nothing distasteful in it as a means of communication between two busy people who are mutual strangers, provided that it is courteously phrased, correctly completed, and personally (and legibly) signed. The great majority of cards come, I believe, from persons genuinely interested in the subject of the reprint, and, in my view, they should be honoured, for there is a strong presumption that the recipient will make better use of the information contained in an article if he possesses it in reprint than if he has to consult it in a library.

The reprints fluttering about the world today are a sort of distillate from the bubbling cauldron of medical literature; they will come down, according to their contents, at the most suitable concentration points, in the offices and laboratories which have some affinity with their place of origin. It is a privilege to play a part in this process, concentrating knowledge where it can best be used, and the cynical, though entertaining, attitude of your correspondents of Feb. 18 is out of place.

All authors, however, are faced with the practical difficulties of forecasting the demand and, if the number of reprints that has been ordered falls short of the number of requests, of choosing where to send the available copies. An accurate forecast can never be made except in the case of a series of papers on a fairly specialised field published successively in the same journal. I have, in recent years, minimised the second difficulty by acting on the tip of a colleague and delaying the despatch of any reprints until the flow of request cards has virtually ceased—say, three or four months after the article's publication. There is thus time to sort the requests, if numerous, into groups for successive mails. The first reprints go to those whose personal interest in the subject is known and to authors quoted in the article. The next group is sent in response to cards coming from persons or places of generally high repute and also perhaps from corners of the globe that one feels it would be suitable to enlighten. The last group of cards to be considered are those that fail to reveal evidence of their sender's special interest in the topic. It is not always wise, however, to reject the seemingly avaricious card that asks for "other relevant papers"; it may represent the first declaration of an ardent convert.

Finally, Sir, while it may be a nice compliment to send a reprint to a close friend or colleague before he has asked for one, unsolicited copies distributed to those of more tenuous connection are liable to be interpreted as advertising matter and dealt with in an appropriately summary fashion.

Department of Pathology,
University of Sheffield. D. H. COLLINS.

SIR,—Your correspondents are reviving a dispute which was discussed a few years ago in the *New England Journal of Medicine*—whether our standards of propriety demand that a personal letter be written to solicit the favour of a reprint. The discussion was not conclusive, for it seems that there are two kinds of people: the one kind will tolerate the most impersonal request, often grateful that they can leave the satisfaction of the demand to a secretary; the other demands that its ego shall be flattered by the receipt of a personal letter.

There is a temperamental difference between the man who is too interested in his work to worry about formality, and he who is unable to work without a certain modicum of formality and even deference. I do not think that either is necessarily the better, though I confess to greater sympathy with the less formal.

For my part (and I must have received several thousand requests) I am quite relieved to receive postcards, for they are dealt with by my secretary and require little effort on my part. Many of the cards I receive are from people whom I know personally; I certainly do not want them to waste their secretary's time, and their institution's money, by writing me formal letters which will raise my hopes only to cast them down again—for I often enjoy correspondence with my colleagues abroad. I make only one reservation: that only for special reasons will I ask for a reprint of an article published in a British journal, and I expect my British colleagues to do the same—unless, of course, the article is expressly didactic.

London, N.W.10. GEORGE DISCOMBE.

SIR,—I feel obliged to defend the hard-pressed printed reprint request forms. The fact that there is a certain business activity in this matter ought not to influence the reaction towards serious scientific workers and abstract writers. I have myself used these cards for several years and they have been an invaluable help because of my limited secretarial assistance. I have also received many such cards from all over the world and always done my best to answer them as rapidly as possible, with photocopies whenever reprints were exhausted. I have never had the impression of being the victim of stamp collectors or American reprint business firms. Today I put the cards received one upon the other and measured a height of 12 cm. from the past two years.

I must thank many British workers because they have answered promptly my requests. And I cannot see why there should be any serious difficulty in distinguishing between an earnest request and a bogus one, because most reprint cards are printed with the name of the institution where the inquirer works. This makes it possible to limit reprint distribution to institutions of recognised reputation. If only personal letters were answered, it would be much more time-consuming, and more costly in postage, too, to get the reprints necessary for scientific work today. Alone in such specialised fields as bile-pigments and porphyrins, which I do what I can to cover, my files for the past few years run into several hundred reprints. With all the new journals appearing the need for this reprint service becomes every day increasingly important.

I agree with Dr. Farnan (Feb. 18) that the French rarely send reprint cards. Among my 12 cm. pool I could find only one from France, from Hôpital Hérold, Paris, 19e, printed in French with English below.

The Swiss idea quoted by Dr. Lenihan (Feb. 18) is certainly a very good one and ought to be widely used. Many American institutions have a reply card of the form: "Sorry our supplies of reprints of . . . requested by you are exhausted. Sincerely yours . . ."

County Hospital,
Svendborg, Denmark. TORBEN K. WITH.

SIR,—Mr. Northfield's letter last week is clearly that of a senior consultant working in a famous teaching hospital which no doubt itself maintains a fairly comprehensive library.

He himself is a fellow of a society, situated only a few miles from his hospital, which maintains a larger journal subscription than any other medical library in the country. Furthermore, any of its journals published in this century are available on loan to fellows. I imagine that many of those whose requests for reprints he finds so irritating work in quite small towns where the journals in which he writes are by no means so easily available, or else the demand for the single volume taken is such that it is almost constantly on loan. Such is the situation

in the only library in this region which makes any attempt at being comprehensive—the Medical School Library. This library has, therefore, decided to cease lending journals (except overnight); thus the staff of all the hospitals in the region more than 5 miles from Birmingham can obtain journals (except the few taken by their hospitals) only by post from libraries in London. It is impossible to keep abreast of the expanding world medical literature by this means.

May I ask those who make important contributions to medical knowledge, to be tolerant of those who seek to benefit or help others to benefit from their observations by requesting a reprint, even though they endeavour to lessen the postal and secretarial expense by using cards instead of letters. The case of requests from librarians has been most cogently put by Mr. Brunning (Feb. 25).

Clearly the number of reprints ordered must be tailored to the budget of the institute in which the author is working. If, however, the number purchased and distributed is deliberately restricted out of annoyance with the unknown senders of anticipated requests, the author must surely to some extent defeat his original purpose in writing the article—namely, the spread and sharing of scientific knowledge. He may even be thought to be working against the spirit of the times in which such dissemination of information plays so important a role.

Midland Centre for Neurosurgery,
Smethwick Hospital,
Smethwick.

A. L. WOOLF.

SIR,—Having recently received a batch of ten printed cards each requesting a reprint of the same paper and all addressed in the same handwriting on behalf of ten individual doctors from a well-known American medical centre, I can appreciate Dr. Faulds' feeling that guidance is needed. Similarly one is disinclined to comply with an unexplained request for more than one reprint. Absence of a signature merits a negative response, and so also does an illegible signature unless the name is printed or typewritten in addition—alternatively an illegible signature may be cut out and fixed to the reply envelope.

On the other hand, Dr. Faulds' irritation has evidently spread to encompass matters which should give no offence. A request should surely not be ignored simply because it has come from a non-medical person, from an unfamiliar institution, or even from an American institution. An inundation of reprint requests is a sign that the paper has aroused wide interest and this should afford pleasure rather than cause vexation. I suggest that Dr. Faulds adopt a liberal policy even at the risk of treating some supplicants better than they deserve.

The propriety of using printed request cards has been called in question; it seems that these cause especial annoyance and frustration to Dr. Farnan (Feb. 18). The multilingual card is possibly rather condescending in that it assumes ignorance of elementary French and German, but I find nothing discourteous in a suitably worded card, properly completed, legibly signed, and correctly addressed. The use of these cards is both convenient and economical.

Glasgow, W.1. A. J. WATSON.

SIR,—My trouble is that most of my reprints are left on my hands, unlike Dr. Faulds. It is difficult to understand why requests for them should annoy some authors (Dr. Farnan and Dr. Lenihan), instead of pleasing them that others find their work valuable.

Recently I had a request from Italy, in English, French, Italian, German, and Spanish, with the name of the sender and that of his university printed on the card. From this and others, it appears that some persons are in the habit of sending such requests in numbers. The reason for this is obscure—perhaps because it is easier than to transcribe from a journal in a library—but it should not be difficult to elucidate it.

I suggest to Dr. Faulds that before sending reprints to unknown petitioners he write to ask them why they want them and that if, through this, the mystery be unveiled he write again to you, Sir, to let us know the secret.

Gaillimh, Ireland. S. UA CONCHUBHAIR.

SHORTAGE OF HOSPITAL STAFF

SIR,—Miss Wood (Feb. 11) stresses the need for good publicity for the professions supplementary to medicine and for talks given by those able to speak from first-hand experience. Recognition of this need has always been the basis of the public relations work of the Nursing Recruitment Service. The staff, all of whom are State registered nurses, speak to some 175 groups annually, either of pupils or of members of parent-teacher associations or similar organisations. In addition they write or provide information for articles in many magazines.

It is impossible to calculate the numbers of people reached in these ways, but over 5000 new and definite inquiries about nursing are received annually, in addition to those from girls under fifteen years of age, which are fully answered but not always recorded or followed up. To date over 33,000 of the Service's candidates have been accepted for training, either for registration or enrolment—an average of about 1650 a year. For the past two years this figure has exceeded 1800 annually. Comments from candidates themselves, as well as from parents and teachers, bear out to the full the experience of your correspondent—that those who have themselves found satisfaction in their work are the people best suited to attract others to it.

LILIAN M. DARNELL
Secretary, Nursing Recruitment Service,
King Edward's Hospital Fund for London.
21, Cavendish Square,
London, W.1.

EXTERNAL CARDIAC MASSAGE

SIR,—The recent correspondence on external thoracic compression as a method of cardiac massage prompts me to record the following incident.

I was giving a man of 55, in good general condition, some ^{131}I-labelled polyvidone into the right antecubital vein when he said he felt " queer ", and collapsed completely. Attempts to give intravenous adrenaline failed. Pulse and respiration were now imperceptible and he was deeply cyanosed. A needle was inserted into the precordium medial to the apical region and about 1 ml. of 1:60,000 adrenaline injected. This was ineffective; the needle (no. 1 Record fitting) was probably too short to penetrate far into the heart-muscle. Another 1–2 ml. was injected; and a nurse was sent for a knife. At this juncture the man appeared dead.

His epigastrium looked to be full, as if his heart had stopped in diastole (probably an entirely false observation); so I gave him a punch in the epigastrium, upwards and to his left, trying to get my fist under the rib margin. Immediately his colour returned, his pulse restarted (at first irregularly), and he began to breathe. He seemingly recovered completely. I could detect no mental abnormalities subsequently; and he was well when I saw him 7 months later.

I cannot prove that his heart stopped; but, at the time, he seemed dead. And the contents of the syringe from which I attempted injection into his heart did not pulsate. The period of complete collapse cannot have been less than one minute, and may well have been two minutes or more.

The case was not efficiently managed—I was taken by surprise. But the satisfactory outcome (if you believe the heart was arrested) leads me to recommend a firm blow to the epigastrium as a primary method of resuscitation.

The polyvidone was kindly supplied by Dr. R. Gordon, Bethesda, Maryland, U.S.A.

Dublin. J. B. HEALY.

STERILISATION

SIR,—Your reports of the symposium at Newcastle on Responsibility in Hospitals (Jan. 28) and of the meeting of the Central Sterile Supply Club in Cambridge have stimulated correspondence (Feb. 4 and 18), particularly on the administration and staffing of central sterile service departments (C.S.S.D.S).

I have been quoted as suggesting that the pharmacist is a suitable member of the hospital team to play an important role in developing the supply of sterile products for medical and surgical treatment. I would therefore like to explain why I have drawn attention to this service which can be rendered by the pharmacist. As I said in Newcastle, our function would be to undertake the technological processes for producing materials and packs of sterile products required by surgeons, physicians, or nursing staff, subject to regular bacteriological examination by the pathologist.

By reason of his academic and practical training the pharmacist regards sterile supply as a natural function of pharmaceutical departments, in which the C.S.S.D. should be integrated as a subsection in the same way as production units for sterile medicaments and galenicals, and supply sections for drugs, surgical dressings, and, in many cases, surgical instruments, already are. I do not wish to suggest that the problems of supplying sterile syringes, instruments, catheters, drip sets, cut-down sets, and dressings are easy; but they present no greater difficulty to the pharmacist than the manufacture of the many intravenous salines, injections, powders, and oils which he is expected to make and supply already, for the simple reason that the universities and colleges of advanced technology have for a long time been training the future registered pharmacists for this very work.

Not to integrate the C.S.S.D.S into the pharmaceutical departments or coordinate their activities with the similar work already being undertaken, would be to waste the existing or potential trained technologists available to hospitals, and already equipped or being equipped by their university or technical college training for this particular work. Complementary work is being undertaken through the department of pharmaceutical sciences of the Pharmaceutical Society, which will already be well known to those active in the field of sterilisation.

As for selecting a title such as " C.S.S.D. manager " for those with no clearly defined training or qualifications for this work, hospital management authorities have, in the Whitley Council structure, already clearly defined the grade of pharmacist who would assume this responsibility—namely, a senior pharmacist. This grade is required to be in charge of a special section, such as the sterilising department or manufacturing laboratory of the pharmacy. With this control, apart from a clerical assistant for recording the stock, normal requirements would be the equivalent of female factory-hands with a capable supervisor, and portering staff who, when employed as steriliser attendants, would be paid the usual rates for the job. Once the pharmacist has decided upon the pack, containers, sterilising process, and labelling, the process becomes repetitive routine production coupled with internal inspection and bacteriological sampling control, naturally coordinated with the bacteriological department.

In the pharmacy, output may involve a simple product such as sterile liquid paraffin or a more complex preparation such as compound injection of sodium lactate; so also in the C.S.S.D. there would be simple products, such as a catheter, or more complex multiple packs, such as those for midwifery.

Others have commented on the extreme flexibility of the designs suggested for C.S.S.D.S which are adapted for fairly rapid change. The C.S.S.D. of today will bear little similarity to that of ten years hence except in its main function of supplying sterile materials for treating human disease by syringe or dressing. Internal production will give way, gradually or rapidly, to commercially produced articles, the quality and price of which will rival anything that the smaller hospital can produce. I refer, of course, to sterilisation by ethylene oxide and gamma radiation, which is essentially restricted to industry. Production space for syringes, dressings, scalpels, surgeons' gloves, catheters, and infusion sets in a hospital will eventually become storage space for an increasing range of commercial articles. C.S.S.D.S will almost certainly continue to produce items made up of cheap basic materials like water and saline because of the relatively high cost of transport from factory to hospital.

C.S.S.D.S can only lead to substantial economies if they are wisely planned and properly staffed, so that controlled routines relieve the professional and qualified hospital personnel from tasks which interfere with their fundamental duties.

Pharmaceutical Department,
Newcastle General Hospital,
Newcastle upon Tyne.

W. T. WING
Chief Pharmacist.

FOOD-POISONING

SIR,—Your annotation of Feb. 18 is informative and timely, and we are indebted to you and to the *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* for annual and many other reports on matters relating to food-poisoning. We would agree we have much to learn about these infections, but we would dissociate ourselves from " the apathy of our fellow-citizens " most emphatically, since we are actively engaged in the education of those concerned with food-handling.

For over three years, in an ever increasing number of centres, from Aberdeen to Cardiff and from Glasgow to Brighton, my Council has been responsible for the introduction of certificate courses in food hygiene and the handling of food. We have been gratified and stimulated to further efforts, not only by the great and continued response at our selected centres, but by the great interest shown by all those attending the courses and by the high pass-rate in the examinations. We have attracted many from the catering trade, from the food industry's many branches, and from hospital and local-authority staff.

Our lecturers include medical officers of health, bacteriologists, and senior food inspectors. We shall be pleased to help all who are interested in this work. The size of the problem calls for our best efforts.

The Royal Institute of Public
Health and Hygiene,
28, Portland Place,
London, W.1.

J. C. AINSWORTH-DAVIS
Chairman, Executive Council.

POSITIONING FOR GALLBLADDER SURGERY

SIR,—In his letter (Feb. 11) Mr. Fauset Welsh does not mention the approach from the patient's left side with the patient supine.[1]

I think that this must mean that he has not given this approach a fair trial, since my experience with it over the last 9 years suggests that it makes operations on the gallbladder and bile-ducts as easy and as safe as possible. Senior registrars and registrars who have gained experience of this approach when working with me have said that they would not wish to return to the difficulties of the right-sided approach. As Mr. Welsh points out, these difficulties are partly due to the gallbladder being concealed under the rib cage on the right side; approach from the patient's left side, through a median incision, enables one to get as high as possible in the abdomen and to see and work under the right costal margin without

1. Haxton, H., McVerry, E. A. *Brit. J. Surg.* 1956, **44**, 147.

difficulty. In addition, the advantage of being able easily to get the fingers of the left hand behind the bile-ducts contributes much to the facility and safety of operations on them.

Like Mr. Welsh, I have seen troublesome back complaints resulting from patients being jacked up on a gallbladder rest, and I should have thought that torsion of the spine under anæsthesia, as advocated in his letter, might also result in back strain.

Manchester. HERBERT HAXTON.

BEHAVIOUR THERAPY IN A CASE OF TRANSVESTISM

SIR,—In view of the success claimed by Raymond [1] in treating a case of fetishism by aversion therapy, we decided to treat a transvestist along similar lines. To the best of our knowledge this is the first attempt to do so.

An otherwise healthy man, aged 22, had frequently dressed in female clothing since the age of 8, latterly 3–4 times a week, and had occasionally appeared in public in his wife's attire. Fear of the consequences, and anxiety to save his recent marriage, finally induced him to seek psychiatric assistance, although sexual adjustment with his wife had always been satisfactory in spite of dressing-up. A 2-year period abroad with the Forces, when opportunities for indulging in transvestism had been much reduced, had not eliminated the symptom spontaneously.

Before treatment several 35 mm. colour transparencies of the patient in female clothing were taken, and a tape-recording was made of him describing the process of dressing-up. The method outlined by Raymond was closely followed. Apomorphine hydrochloride (gr. $^1/_{20}$–$^1/_6$), which was the mainstay of the treatment, was injected intramuscularly 2 hourly for 6 days and nights. Emetine hydrochloride (gr. $^1/_2$) intramuscularly was substituted on a few occasions after apparent tolerance to apomorphine. As soon as the injection was acting—the patient usually reported a headache, then nausea—a slide was projected on a large screen at the foot of his bed and the tape-recording started, and this continued until he either vomited or became intensely nauseated. Dexamphetamine sulphate (5 mg.) was given every few hours throughout the procedure to enhance conditioning through its stimulant properties. Throughout treatment a psychiatrist/psychologist team was in constant attendance and special nursing facilities were provided.

The patient's general condition remained excellent throughout. When treatment was completed, he expressed revulsion at the pictures and at the idea of dressing in female clothing. When interviewed 3 months afterwards he was still apparently cured, was indifferent to the clothes which had formerly excited him, and had lost all desire to dress-up. He regarded transvestism as a "ghastly nightmare" and wished to repress all memory of it, resenting anything or anybody that reminded him of it. As a result he refused to consider the short "booster" course of treatment which Raymond recommended.

The method used can readily be criticised despite its apparent therapeutic efficacy. It is time-consuming and expensive, and is extremely unpleasant for the patient. It is clumsy, for using emetic drugs creates great difficulties in timing the introduction and cessation of the conditioned stimulus (slides and tape-recording) for optimal conditioning, and possibly in some trials the stimulus preceded pleasant rather than unpleasant drug responses owing to fluctuations in the degree of nausea as reported by the patient. Also apomorphine, which has central depressant properties, reduces the value of the conditioned stimulus at the time of presentation, and tolerance develops rapidly to this drug which had to be administered in increasing doses to produce any effects. By contrast, emetine, which is not a central depressant, would appear to be more suitable, but this patient developed tolerance to it also, and its frequent administration is undesirable because of possible cardiovascular sequelæ.

Because of these numerous difficulties it is clearly misleading to regard this procedure as straightforward deconditioning, and at present we are unable to demonstrate the precise mechanisms which alleviated symptoms in our patient.

J. C. BARKER
J. G. THORPE
C. B. BLAKEMORE
N. I. LAVIN
C. G. CONWAY.

Downview and Banstead Hospitals, Sutton, Surrey.

1. Raymond, M. J. *Brit. med. J.* 1956, ii, 854.

ROLE OF THE ERYTHROPOIETIC HORMONE

SIR,—We should like to comment on Dr. Penington's interesting article (Feb. 11). His discussion omits reference to some important work, and we feel his remarks were in places somewhat misleading.

After considering erythræmia accompanying renal carcinoma, hydronephrosis, and polycystic kidneys, he concluded: "More definitive studies will be required in such subjects before the significance of these *clinical associations* can be assessed." Lawrence and Donald [1] found renal carcinoma in 0·93% of 325 polycythæmic patients, whereas the expected overall incidence in America is 0·003%. More than 60 examples of this association have been recorded.[2 3] In many cases the erythræmia disappeared after the diseased kidney was removed. Reappearance of the erythræmia sometimes coincides with a recurrence of the neoplasm.[4] It therefore seems reasonable to regard this clinical association as significant.

There is considerable evidence that erythropoietic substances play a part in renal erythræmia. Gurney [5] demonstrated "erythropoietin" in an extract of a renal carcinoma from a patient with erythræmia. He also found high erythropoietic activity in fluid from a polycystic kidney removed from another erythræmia patient. Nixon and his colleagues [2] found "erythropoietic activity" in the cyst wall and fluid of a solitary renal cyst from a man with erythræmia. These two groups of workers assayed erythropoietin by techniques involving augmentation of ^{59}Fe utilisation in polycythæmic mice and rats respectively. Hewlett and his coworkers,[6] by measuring ^{59}Fe utilisation in starved rats, showed increased erythropoietic activity in extracts of a renal carcinoma associated with erythræmia, as compared with extracts of a similar tumour not accompanied by erythræmia. Whenever plasma was assayed in the above studies, erythropoietic activity was not found to be significantly increased. We have recently studied a further patient with unilateral hydronephrosis and erythræmia.[7] Erythropoietic activity was shown in the sac fluid and in the plasma by an assay technique involving reticulocytosis in normal rats. As we have observed before,[3] the relationship between erythropoiesis and the kidney is far from clear and much further work is needed.

With this uncertainty about the role of erythropoietic substances, consideration of assay methods is obviously vital. In his article, Dr. Penington once again raises possible objections to methods relying on reticulocytosis as the index of response. He suggests that hæmolysis in the assay animal may cause the reticulocytosis. The data in the accompanying table indicate that this is unlikely.

He also suggests that the ether-soluble factor of Linman et al.[8 9] was responsible for the reticulocytosis in our assay. Dr. Penington believes that this factor results from marrow

1. Lawrence, J. H., Donald, W. G., Jr. *Ann. intern. Med.* 1959, **50**, 959.
2. Nixon, R. K., O'Rourke, W., Rupe, C. E., Korst, D. R. *Arch. intern. Med.* 1960, **106**, 797.
3. Jones, N. F., Payne, R. W., Hyde, R. D., Price, T. M. L. *Lancet*, 1960, i, 299.
4. Omland, G. *Acta med. scand.* 1959, **164**, 451.
5. Gurney, C. W. *Trans. Ass. Amer. Phycns.* 1960, **73**, 103.
6. Hewlett, J. S., Hoffman, G. C., Senhauser, D. A., Battle, J. D., Jr. *New Engl. J. Med.* 1960, **262**, 1058.
7. Payne, R. W., Jones, N. F. Unpublished observations.
8. Linman, J. W., Bethell, F. H. *J. Lab. clin. Med.* 1957, **49**, 113.
9. Linman, J. W., Bethell, F. H., Long, M. J. *Ann. intern. Med.* 1959, **51**, 1003.

HÆMOGLOBIN LEVEL AND RETICULOCYTE COUNT AFTER INTRAPERITONEAL INJECTIONS

Intraperitoneal injection (2 ml.)	Response 72 hours after injection	
	Hæmoglobin (% Haldane)	Reticulocytes (% of red blood-cells)
Isotonic saline ..	91, 94, 94, 101 } 95·0% (±4·3%)	1·8, 1·8, 2·4, 2·5 } 2·1% (±0·4%)
Cobalt chloride 3 mg.	91, 94, 96, 101 } 95·5% (±4·2%)	4·2, 6·0, 6·4, 7·0 } 5·9% (±1·2%)
Plasma from anæmic patients	91, 94, 94, 94 } 93·3% (±1·4%)	3·7, 4·0, 4·0, — } 3·9% (±0·2%)

proliferation, and that it is "distinct from the erythropoietic hormone both chemically and biologically (Penington 1960)", whereas Linman et al.[9] concluded that this factor is "not a by-product of hyperactive myeloid elements". The reference "Penington 1960" is to a letter[10] quoting unpublished work, and a firm conclusion seems premature; indeed, we find it difficult to understand how he concluded from the information at his disposal that these two agents were "*primarily*" responsible for the reticulocytosis in our assay (see Payne [11 12]).

The use of ^{59}Fe uptake to assay erythropoietin also has possible disadvantages. Jandl et al.[13] showed that circulating reticulocytes can take up iron from the blood. A falsely high value for ^{59}Fe utilisation might therefore be obtained if the assay material produced a reticulocytosis before the ^{59}Fe was given. Furthermore, a value for the blood-volume must be used in the calculations; deriving this value from the weight is imprecise; and calculation from ^{51}Cr red-cell volume may also be unsatisfactory in animals rendered polycythæmic by transfusion, which may cause variation in the venous-hæmatocrit: body hæmatocrit ratio.

We conclude that assay methods for erythropoietin(s) are still imperfect. Much interest therefore attaches to the study by several groups of American workers reported by Keighley et al.[14] They compared many different assay systems simultaneously using the same potent plasma extract. Augmentation of erythropoiesis was obtained in intact, starved, or polycythæmic rats or mice, whether judged by a rise in hæmoglobin concentration, hæmatocrit, ^{59}Fe utilisation, or reticulocytosis. We hope that further similar cooperative studies will be undertaken; until pure erythropoietin, or erythropoietins, is available dogmatic assertions are not in our view justified.

St. Thomas's Hospital, London, S.E.1. R. W. PAYNE, N. F. JONES.

BENCE JONES PROTEINURIA

SIR,—In their excellent paper on myelomatosis (Feb. 4), Dr. Innes and Dr. Newall state that the presence of Bence Jones proteinuria proves the diagnosis. It may be questioned, however, whether this is strictly correct.

According to a number of reports,[15–18] this form of protein is occasionally to be found in the urine of patients with other disorders including lymphatic and myeloid leukæmia, skeletal carcinomatosis, multiple sarcomas of the bone, and polythycæmia. In this connection, it may be recalled that Meyler [19] succeeded in isolating Bence Jones protein from normal bone-marrow; as he also detected it in the pus of abscesses and in the leucocytes of patients with leukæmia, he concluded that the white cells were concerned in its production. Meyler suggested that the amount of Bence Jones protein provided by destruction of either the leucocytes (e.g., leukæmia) or the bone-marrow (e.g., skeletal metastases) is almost always sufficiently limited for it to be broken down in the body, whereas in myelomatosis the plasma cells often synthesise so much of this material that some of it escapes degradation and is excreted in the urine.

Medical Research Laboratories, Charing Cross Hospital, London, W.C.2. M. A. PEYMAN.

PYELONEPHRITIS

SIR,—We were interested to read the paper by Dr. Hutt and his colleagues (Feb. 18). Several points, however, deserve special comment in connection with the attempt to recover the infecting organism:

(1) The authors state that the urines were plated for culture on MacConkey's medium. This medium is good for intestinal bacteria but is a well-known suppressor of many non-intestinal organisms particularly if, as in this series of cases, the organisms may already have been at a disadvantage because of their exposure to antibiotics. It is always advisable to plate out the centrifuged deposit on a blood-agar medium as well as MacConkey's, as these two media between them will permit the growth of most organisms found in urine, apart from such genera as mycobacterium and leptospira.

(2) In order to minimise the effects of antibiotics it is wise to use liquid culture media to supplement the solid media.

(3) Stained films of the deposit should be examined for the presence of bacteria, especially with catheter specimens, and the results correlated with the cultural findings.

Institute of Pathology, The Royal Infirmary, Cardiff. P. CALLAGHAN, R. A. HOLMAN.

METRIC SYSTEM IN PRACTICE

SIR,—We should like to bring to your notice the fact that at University College Hospital the metric system was introduced exclusively in January, 1957, after a year's notice during which it and the apothecaries' system were used side by side. The advantages and difficulties were outlined in the *Nursing Times* (Jan. 25, 1960) by one of us (T. D. W.), and Sister G. F. Schofield in the same issue gave the nursing point of view. In our experience the changeover can be easily adopted provided there is cooperation and not silent resistance.

In last year's symposium on the metric system at the British Pharmaceutical Conference, Dr. K. R. Capper [1] stated that this hospital had adopted the metric system more completely than any other in the United Kingdom by using rational metric quantities—e.g., 100, 50 mg., &c.—instead of mere equivalents of apothecaries' doses.

Students in their preclinical studies are invariably taught in the metric system but have the additional burden of learning an obsolete system in their clinical years. This country is the only one in Europe and soon in the Commonwealth that still adheres to archaic measures. It is obvious that for international communication and our export trade we cannot afford to be out of step with the rest of the world.

Obstetric Hospital, University College Hospital, London, W.C.1. T. D. WHITTET, Chief Pharmacist, W. C. W. NIXON.

SIR,—Your annotation on the forthcoming adoption of the metric system by the *British Pharmacopœia* in 1963, is a timely one. It is perhaps debatable, however, whether the public will ever be persuaded to give up inches, feet,

10. Penington, D. G. *Lancet*, 1960, i, 975.
11. Payne, R. W. M.D. thesis, Cambridge University, 1960.
12. Payne, R. W. *Brit. J. Hæmat.* (in the press).
13. Jandl, J. H., Inman, J. K., Simmons, R. L., Allen, D. W. *J. clin. Invest.* 1959, **38**, 161.
14. Keighley, G., Lowy, P. H., Borsook, H., Goldwasser, E., Gordon, A. S., Prentice, T. C., Rambach, W. A., Stohlman, F., Jr., Van Dyke, D. C. *Blood*, 1960, **16**, 1424.
15. Boggs, T. R., Guthrie, C. G. *Johns Hopk. Hosp. Bull.* 1912, **23**, 353.
16. Geschickter, C. F., Copeland, M. M. *Arch. Surg.* 1928, **16**, 807.
17. Magnus-Levy, A. *Z. klin. Med.* 1932, **119**, 343.
18. Bayrd, E. D., Heck, F. J. *J. Amer. med. Ass.* 1947, **133**, 147.
19. Meyler, L. *Arch. intern. Med.* 1936, **57**, 708.
1. *Pharm. J.* 1960, **185**, 229.

and yards, or ounces, pounds, and stones. However desirable and simple the metric system may be, it contains one inherent and ever present danger—namely, the shifting of the decimal point in the wrong direction. There have been many fatalities, one only a few months ago, where owing to a wrongly placed decimal point doses of drugs ten times too great have been given.

This brings up the question, why if this point is so important, is it so insignificant? Surely, before it is too late, the decimal point should either be increased in size so that it is clearly visible or replaced, as in some continental countries, by a stroke. Thus 1·5 mg. becomes 1|5 mg. Or some alternative device might be adopted to render accidents less liable to occur. It is to be hoped that the standing committee of the *British Pharmacopœia* will give serious consideration to this suggestion.

London, W.1. MASSEY DAWKINS.

TRIAL OF TRAVEL-SICKNESS REMEDIES

SIR,—A clinical trial of travel sickness remedies is being organised by the physiology department of the London Hospital Medical College (head of department, Prof. K. W. Cross).

The subjects are to be doctors' own children, travelling on ordinary car journeys. The substances to be tested are all widely used and known to be quite safe. Children between the ages of four and eleven are needed.

We have already made an appeal for help to the members of the College of General Practitioners. In order to widen the scope of our sample we should be grateful for any doctor, who has children who are regularly car-sick and within the trial age range, to send a postcard mentioning the number of children he has within this category, to the address below.

This will not commit him in any way but detailed plans of the experiment will be forwarded and the doctor may then decide whether he would be prepared to help in the trial.

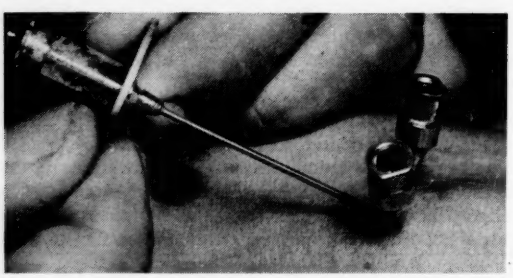
Department of Physiology, The London Hospital Medical College, Turner Street, London, E.1. C. L. BRAY M. S. HALL.

A SIMPLE TECHNIQUE FOR ARTERIAL PUNCTURE

SIR,—Percutaneous arterial puncture is now a routine procedure. The peripheral arteries—brachial, radial, and femoral—are commonly used during cardiac catheterisation and arteriography, whereas the carotids and vertebrals are needled for cerebral angiography.

In assessing respiratory function the determination of the arterial oxygen and carbon-dioxide tensions is as necessary and obligatory as estimation of the blood-urea in renal disease.

One of the main technical difficulties of percutaneous puncture is the mobility of the arteries, especially the brachial, despite external methods of stretching and fixing them. For the past two years, in the occasional difficult case, we have used a simple internal method for fixing and immobilising the brachial artery. A similar method can be applied to other arteries, and can be used in the ward or surgery.



After localising the artery by external palpation and splinting the limb, the overlying skin is infiltrated with local anæsthetic. A fine (21 or 22 gauge) hypodermic needle is then inserted through the skin and deep fascia on either side of the artery, thus immobilising the vessel (see figure). A sharp arterial needle can then be inserted percutaneously into the immobilised artery without difficulty.

This study has received support from the C.S.I.R. and City Council of Cape Town.

Groote Schuur Hospital and C.S.I.R. Cardio-Pulmonary Group, University of Cape Town, South Africa. B. KAPLAN V. SCHRIRE.

MORTALITY FROM CORONARY HEART-DISEASE IN INDIAN POPULATIONS

SIR,—When a Western diet and mode of life are progressively adopted, an accompanying rise in mortality from coronary heart-disease (C.H.D.) has often been noted. This has been well described in Japanese immigrants to Honolulu and California by Keys and his associates, and in Yemenite immigrants to Israel by other workers. But it is not generally appreciated that the most dramatic increases in mortality are in Indian migrants to other Eastern or African territories.

In India among the very poor virtually no deaths are caused by C.H.D.; but among the wealthier merchants and professional classes deaths from this cause are not uncommon, though the mortality-rate is possibly lower than in most White populations.[1] C.H.D. has, however, been shown to be very common among Indians in Singapore, accounting for about 50% of all heart-disease over the age of 20,[2] and the annual mortality-rate rising to 255 per 100,000 in the 50–59 year age-group. In Central Africa, at Kampala in Uganda, C.H.D. in Indians over the age of 30 is reported to account for no less than 43% of male deaths and 9% of female deaths.[3] For comparison, in New York, with one of the highest mortality-rates from C.H.D., in 1955 all heart-diseases were responsible, in those over 25, for 50% of male and 46% of female deaths; slightly more than half these deaths were from C.H.D.[4] The reason why fewer Indian women die of C.H.D. in Kampala is not clear, although one factor must be their lower life-expectancy as compared with New York women. But it would seem that C.H.D. is more lethal to Indian men in Kampala than to any other population anywhere in the world. Among Indians in South Africa too, C.H.D. mortality is high. In Durban, with over a quarter of a million Indians, C.H.D. mortality appears to be approaching that of the South African whites,[5] and their mortality-rate is stated to be second only to that of the U.S.A.[6] The high mortality among Durban Indians is unexpected, since over three-quarters of them are regarded as very poor. To clarify the local situation, and the ætiology of the disease, we are making observations (diet, blood-pressure, electrocardiographic appearances, blood-biochemistry, &c.) on Indian populations—Hindu and Moslem—in Johannesburg and Pretoria.

A number of points deserve comment.

(1) The diet of African Indians is not a "westernised" diet in the orthodox sense. In Uganda, the diet includes polished rice, wheat flour (for "chapatis" and "pooris"), lentils ("dhal"), fruit, and vegetables, with variable amounts of eggs, fish, and meat, depending on whether they are Hindus (mainly milk-and-egg vegetarians) or Moslems. The fat includes approximately 2 oz. cottonseed oil, and $2^1/_2$ oz. butter fat (as

1. Padmavati, S., Gupta, S., Pantulu, G. V. A. *Circulation*, 1959, **19**, 849.
2. Danaraj, T. J., Acker, M. S., Danaraj, W., Wong, H. O., Tan, B. Y. *Amer. Heart J.* 1959, **58**, 516.
3. Shaper, A. G., Jones, K. W. *Lancet*, 1959, ii, 534.
4. City of New York, department of health. Summary of vital statistics, 1955.
5. Cosnett, J. E. *S. Afr. med. J.* 1957, **31**, 1109.
6. Bronte-Stewart, B. *Post Grad. med. J.* 1959, **35**, 180.

"ghee", butter, milk, or cheese) per day, supplying about 30–45% of their calorie intake.[3] In South Africa, the diet-pattern appears *qualitatively* the same, but sunflower oil or other cooking oil is used instead of cottonseed oil. The local Indians say that this diet would be adopted by many in India if the food was available and money to buy it.

(2) The experience with these African Indians would seem to supplement the findings of recent investigations—both experimental [7] and clinical [8]—which point to the harmful role of butter fat in atherosclerosis and mortality from C.H.D. Nevertheless, we must determine whether the noxious influence is independent of the dietary setting. Elsewhere [9] I have suggested that a careful study of African nomadic groups subsisting for the most part on milk (camel's, goat's, sheep's, or cow's) might provide crucial information on the subject. Until results are available we should keep an open mind, since in Africa (and elsewhere) many anomalies arise in predicting nutritional disease—i.e., where certain diseases are less common than might be expected, and vice versa.[10]

(3) In view of the current interest in vegetable-oil prophylaxis, the very high mortality from C.H.D. on a diet including a liberal amount of this oil is noteworthy.

(4) I do not, of course, intend to imply that diet is the only factor in these changes in C.H.D. in Indian populations. Immigrant Indian groups are not assimilated into the population of their adopted countries; in Singapore, Uganda, South Africa, and doubtless elsewhere, Indians (over at least two generations) have maintained their own culture. This refutes the view that integration, with its dietary and non-dietary ramifications, as occurs with the Japanese and Yemenite immigrants, is almost a prerequisite for a rise in C.H.D.

Thus among Indian population-groups today we find the widest extremes in C.H.D. mortality. This and the fact that they are a "pure", culturally distinct population, surely makes them a particularly valuable population in which to study the ætiology of coronary heart-disease.

Our studies on the Indian (and Bantu) populations are being supported by a grant from the National Heart Institute, U.S. Public Health Service.

Human Biochemistry Research Unit,
South African Institute for
Medical Research,
Johannesburg.

ALEXANDER R. P. WALKER.

ATHEROSCLEROSIS AND CORONARY THROMBOSIS

SIR,—We were disturbed that Professor Crawford and his colleagues (Feb. 25) felt that comment on their paper (Jan. 28) might lead to confusion. Discussion usually serves to clarify most problems.

We have never implied that thrombosis in man occurs independently of atherosclerosis but have sought to emphasise that the atherosclerotic lesion may not be the only factor in the production of coronary thrombosis. This is in agreement with the observation [11] that in recent years coronary atherosclerosis has decreased but death from ischæmic heart-disease has increased tenfold. Nine of the cases of Professor Crawford and his colleagues in the age-group 32–52 showed this lack of correlation between the extent of atherosclerosis and the occurrence of fatal thrombosis of the lumen. It is in this group of cases that some added factor such as "hypercoagulability" of the blood may be operative to precipitate thrombosis. Such cases serve to explain the increased incidence in coronary thrombosis in recent years, and the statement that the disease pattern in younger men does not differ from that in older men is likely to obscure their significance. We do not regard the age of 52 as being particularly old.

Crawford et al. state (Feb. 25) that in 28 out of 50 consecutive cases aged 60–80 years they found evidence of recent thrombosis. It would be of interest to know if such thrombi were of the type described in their paper as "unorganised fibrin or atherosclerotic debris". This is a term which we implied when referring to the silting up of the fine branches of the coronary arteries (Feb. 18) and is quite distinct from a recent thrombus adherent to an atherosclerotic plaque.

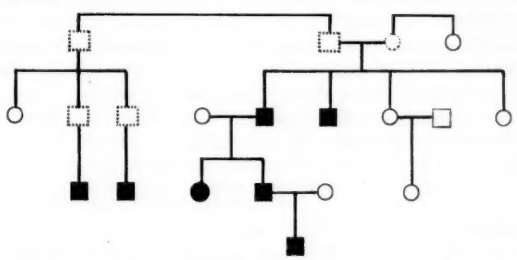
Dr. Mann's comments (Feb. 25) on the present methods available for producing thrombosis in the rat are little more than a "counsel of despair". If all experimental systems leading to toxicity are to be abandoned little progress will be made in experimental pathology. He expresses the opinion that infarction obtained by feeding hypercholesterolæmic substances to rats is related to an increased viscocity and obstruction to the blood-flow produced by the intense lipæmia. Our recent unpublished work disproves this view—experimental thrombosis could be prevented by feeding anticoagulants such as phenindione ('Dindevan') although the intense lipæmia was unchanged.

Department of Pathology,
University of Cambridge.

A. N. HOWARD*
G. A. GRESHAM.

EXTREME INSENSITIVITY OF THE FOREARMS

SIR,—Upon the forearm, a person can normally distinguish two points of a divider when they are between 2 mm. and 10 mm. apart. The following family shows a dominant inheritance of extreme forearm insensitiveness, averaging 220 mm. as the distance of "double-point" appreciation.



There is no known linkage, and I do not believe the phenomenon has been reported before.

Swallowcliffe,
Wilts.

PATRICK F. JAMES.

ORAL PROGESTOGENS

SIR,—Controversies about nomenclature are usually sterile and seldom of interest except to a very few people immediately concerned. We expect that *The Lancet* will not continue for much longer the discussion between Dr. Hewett and ourselves (Feb. 25) as to who attaches what name to which steroid ring. As there is a point of immediate application to the treatment of patients at issue here we might be allowed one reply.

The known masculinising effects of testosterone and the alleged effects of nortestosterone compounds on the female fœtus have given these compounds a bad reputation in gynæcological endocrinology. Hence Messrs. Organon may prefer that these words should not be applied to their product. But it needs to be stated with emphasis that allylestrenol is a nortestosterone in exactly the same sense as acknowledged nortestosterone compounds such as 17α-ethinyl-19-nortestosterone is. The parent company of Dr. Hewett's firm in the Netherlands have made no objection to the description of their product as a nortestosterone in situations where there is no unfounded prejudice against this class of compound. The first major clinical trial of allylestrenol was conducted by H. Willemsen in Holland. It is described as a 19-nortestosterone compound on p. 65 of his M.D. thesis presented at the University

7. Gresham, G. A., Howard, A. N. *Lancet*, 1960, ii, 527.
8. Hartroft, W. S. 5 Int. Congr. Nutr. panel 3, p. 21, 1960.
9. Walker, A. R. P. *Brit. med. J.* 1960, i, 1660.
10. Walker, A. R. P. *Nutr. Rev.* (in the press).
11. Morris, J. N. *Lancet*, 1951, i, 69.

* Member of external staff, Medical Research Council.

of Groningen in 1960. This designation is repeated elsewhere in the Continental literature by Borglin.[1]

We hope that Dr. Hewett's excursions into the relative merits of description in terms of the oestrane ring or in terms of testosterone will not distract attention from the central fact that the compound his company is marketing is a 19-nortestosterone compound. We have no quarrel with the use of oestr-4-en-17β-ol except that it is impossible to say and in print the clinical mind baulks at it. The term 3-desoxy-19-nortestosterone was used by Willemsen and gave us the formula for allylestrenol without reference to the list issued by the General Medical Council. There is a difference of choice, not of fact, between us in the argument about names.

Medical Research Council
Obstetric Medicine Research Unit,
Medical School,
Aberdeen.

A. KLOPPER
M. C. MACNAUGHTON.

SIR HAROLD GILLIES MEMORIAL FUND

SIR,—With the approval of Lady Gillies, the British Association of Plastic Surgeons has opened a fund to commemorate the pioneer work of the late Sir Harold Gillies and to perpetuate his lifelong devotion to the development of plastic surgery and to the encouragement of younger surgeons during their period of training to be plastic surgeons.

It is proposed to endow a fund to provide for:

(1) An annual lectureship on a plastic surgical subject, to be known as the Gillies Memorial Lecture.

(2) Grants to foster education, study, and research in plastic surgery.

Contributions to this fund are invited and should be sent with the name and address of the donor to the Westminster Bank Ltd., 154, Harley Street, London, W.1, marked "Sir Harold Gillies Memorial Fund". An acknowledgment will be sent as soon as possible.

G. H. MORLEY
President,
London, W.C.2. British Association of Plastic Surgeons.

Parliament

Commonwealth and Common Health

IN the debate on Feb. 22 on aid for underdeveloped countries, Baroness SUMMERSKILL asked whether we should be satisfied with our record in social welfare in the Commonwealth. There was urgent work in medicine which we had neglected. Throughout the Commonwealth there were gross inequalities. In some parts there was a struggle for medical work, and precious time was wasted on trivial complaints; in other parts there were large numbers of seriously ill patients with little hope of any medical service. In Britain, a doctor's maximum list was 3500 patients—and even this figure was rightly regarded as too high. In Sierra Leone there was 1 doctor to 26,000 people, in Nigeria 1 doctor to 57,700 people, in Kenya 1 doctor to 10,500 patients, in Uganda 1 doctor to 15,900 patients, and in Northern Rhodesia 1 doctor to 8140 patients.

We should take to the underdeveloped countries medical services which would be widely appreciated and well within our means. No doubt much good was done when our well-meaning missionaries carried the Bible to distant lands; but today the rod of Æsculapius would prove a more formidable weapon. Men and women throughout these countries knew that poverty, hunger, disease, and ignorance could be remedied; and they would incline to the nation which offered them relief and help. Here was an opportunity for the Minister of Health to undertake a task of real nobility. We needed an all-embracing medical plan for teaching and research over the whole Commonwealth. Indeed, if we in this country prepared a plan, it could be regarded as a prototype for other nations throughout the world. Some small attempts had been made by individuals impelled by idealism to meet the needs of the underdeveloped countries; but something more comprehensive was needed which would inspire men and women to give their services abroad. The Prime Minister could raise the matter of a medical service within the Commonwealth at the next Prime Ministers' conference, and a Commonwealth Medical Conference could be organised.

In his reply the Earl of PERTH said that we had over here at the moment 2000 medical students; in the Colonies there were a further 1300 medical students, and in Nigeria 220. It was already perfectly possible for doctors or medical teachers who wanted to go out to be financed from this country (if they were going into public service) under the Overseas Service Bill, which the Government hoped to pass in a short time, or (as medical teachers) under the technical assistance agreements. None the less, this was a tremendously important subject, and he would certainly draw the attention of the Minister of Health to the thought that, whereas education was the subject at the Finance Ministers' Conference at Montreal, we, as a Commonwealth, might now think even more about health.

Tuberculosis and Food-handlers

ON Feb. 21, at the report stage of the Public Health Bill, Lord AMULREE moved to insert a new clause prohibiting people with tuberculosis from handling food. Though the danger of spreading the disease through a food handler was not great, in his view it existed. He suggested that someone who went regularly to the same restaurant for a midday and evening meal might, through getting massive regular doses of tubercle bacillus in his food, eventually suffer by that infection getting into his pulmonary system and giving him pulmonary tuberculosis. People with tuberculosis employed in preparing and cooking food could be a great danger to the colleagues working with them, often in small kitchens. In snackbars a tuberculous assistant handing food across a counter might infect a customer. A waiter with active pulmonary tuberculosis might infect some of his customers.

Treatment for pulmonary tuberculosis was far more satisfactory than it was not long ago; and many people were cured. Therefore we wanted as many people as possible to go into hospitals or sanatoria or even have treatment in their own homes, rather than to carry on working, rather uncomfortably, and infecting the people working around them.

Lord TAYLOR opposed the clause, which he thought was founded on a misconception. Bovine tuberculosis could be spread by milk, but there was no evidence that anything except droplet spray carried infection of other forms of tuberculosis. If Lord Amulree wanted to prevent that, the clause should include cinema usherettes and assistants in any crowded store. There was no reason to single out the food trade. Baroness SUMMERSKILL disagreed with this point of view. Surely the dried sputum of a tuberculosis patient carried infection. Every bus carried a notice saying that the penalty for spitting was £5. Much of our preventive medicine had been introduced because statistically it had been proved that there might be evidence which perhaps pathologically we had not necessarily been able to deduce. She agreed that the clause should also apply to cinema usherettes, but that would be impracticable. Therefore we must do what we always did in this country: adjust our legislation to the needs of the time and do it in piecemeal fashion.

Lord NEWTON said that in the view of the Government's medical advisers there was no special risk of the transmission of disease through the handling of food which would justify singling out in general legislation this particular activity for prohibition to people with tuberculosis. It was generally held by the medical profession that pulmonary tuberculosis was an airborne and not a food-borne infection and that infection was by inhalation rather than by ingestion of droplets. The Public Health Laboratory Service had confirmed that, in their view, there was no danger arising from the handling of food by tuberculous persons. Tuberculous people working in a restaurant,

1. Borglin, N. E. *Acta endocr. Kbh.* 1960, **35**, suppl. 58.

café, bar, or teashop were not any more or less likely to infect people who came into those premises than those who worked in shops or offices or other confined premises. A regular customer with tuberculosis was just as likely to infect other customers as an infected waiter or barman. Lord Newton also agreed that people who had open tuberculosis should not be encouraged to go about too much among the community until they were under proper drug-control, but legal restrictions on their movements could be justified only on the ground of risk to others. It was for their own medical advisers to persuade them to do what was for their own good. Admittedly the provisions of this clause had been included in many local Acts, because it was then believed that tuberculosis was due to an infection of the alimentary tract, but this view had now been superseded in the medical profession.

Lord AMULREE, withdrawing the clause, admitted that he was not entirely convinced by the Government's arguments. He believed that, if people who had open tuberculosis were handling food and serving other people, they were more liable to infect those other people than if they had not got it.

QUESTION TIME

Cost of Prescription Refunds

Mr. G. R. CHETWYND asked the Minister of Pensions and National Insurance what had been the average administrative cost to the National Assistance Board of an application for a refund of the prescription charge; what estimate he had made of the cost when the charge was doubled; and what was his estimate of the additional applications that would be made.—Mr. J. A. BOYD-CARPENTER replied: The estimated total administrative cost of refunds of prescription charges by the National Assistance Board is at present about £145,000 a year. This has to be set against a total amount refunded of £1,066,000 in 1960, and represents rather more than 1½*d.* per 1*s.* prescription item. The increase in the charge should of course tend to reduce the administrative cost in proportion to the amount refunded, since the administrative cost of refunding 2*s.* must be approximately the same as that of refunding 1*s.* Some increase in the number of applications for refunds may be expected.

Refunds of N.H.S. Charges

In 1960 grants made for N.H.S. charges from the National Assistance Board totalled £2,154,000, of which £2,002,000 was paid to people already receiving a regular weekly National Assistance grant and £152,000 to other people.

Consultants and Their Awards

The following table gives the number of consultants in the National Health Service in England and Wales in each specialty and shows the distribution of merit awards:

Specialty	At Dec. 31, 1959				At Dec. 31, 1958			
	Number of consultants	Awards			Number of consultants	Awards		
		A	B	C		A	B	C
General medicine	868	62	160	273	838	61	155	259
Diseases of the chest	295	11	23	58	307	10	27	57
Mental health	648	9	23	62	631	7	23	63
Neurology	79	9	20	23	75	9	19	22
Pædiatrics	209	11	36	54	208	11	32	56
Radiology	463	9	19	72	451	9	18	69
Radiotherapy	120	7	10	21	118	7	10	20
Physical medicine	87	1	1	13	83	1	1	13
Pathology	693	27	49	99	660	25	48	101
Infectious diseases	39	..	4	15	41	..	4	15
Dermatology	144	5	17	26	148	4	18	28
Venereology	77	..	2	13	78	..	3	14
Ophthalmology	303	15	27	46	305	15	26	51
General surgery	864	57	144	261	862	59	144	256
Anæsthetics	795	8	25	81	787	6	24	78
Neurosurgery	58	7	10	16	52	6	9	10
Plastic surgery	56	4	12	14	52	4	9	16
Thoracic surgery	91	10	20	29	88	9	21	28
Orthopædic surgery	333	14	42	74	326	15	41	73
Dentistry	260	5	12	34	260	7	13	34
Ear, nose, and throat surgery	304	10	30	59	303	10	31	60
Obstetrics and gynæcology	439	20	55	120	436	19	54	114

If a consultant practises in more than one specialty, he has been included in each.

Cost of Pharmaceutical Services

The cost of the N.H.S. pharmaceutical services in England and Wales during 1958–59 falls under the following headings:

	£
Payments to dispensing doctors for services and for drugs, appliances, and dressings supplied	2,300,000
Payments to chemists and appliance contractors in respect of:	
(*a*) Dispensing fees and rota services	12,750,000
(*b*) Oncost allowances	10,430,000
(*c*) Allowances for containers	1,370,000
(*d*) Cost of appliances and dressings	2,080,000
(*e*) Cost of prescriptions specifying drugs by standard names	9,180,000
(*f*) Cost of prescriptions specifying drugs by proprietary names	30,450,000
	68,560,000

Payments to chemists at (*a*) and (*b*) constitute payments for overheads, professional services, and profits. The total of payments at (*d*), (*e*) and (*f*) includes an estimated sum of £630,000 for purchase-tax. Wholesalers' margins are estimated to account for £5½ million–£6½ million of the total of the payments at (*d*), (*e*), and (*f*).

Obituary

HAROLD CHARLES CORRY MANN

O.B.E., M.D. Lond., M.R.C.P.

Dr. Corry Mann's investigation into the nutrition of boys of school age attracted much attention when it was made some thirty-six years ago, and in its application it has proved of permanent benefit to the nation.

He qualified from Guy's Hospital in 1903. After holding appointments at Guy's as medical registrar, tutor, and assistant demonstrator in pathology, he decided to specialise in children's diseases, and he joined the staff of the Evelina Hospital for Sick Children. He was also physician to St. Saviour's and St. Olave's grammar schools.

He soon became interested in nutritional problems, and in 1914 published an important paper on the feeding of infants and prevention of rickets. After the war he undertook research work for the Medical Research Council, and his first report in 1922, on environment and diet as causes of rickets, was a continuation of his earlier work. In 1919 the Committee on Accessory Food Factors issued a memorandum stressing the importance of including vitamin-containing foods in all dietaries. Milk had been distributed in some London schools as early as 1908, and in order to obtain further scientific data on the subject the Ministry of Health in 1924 asked the M.R.C. to conduct a field experiment. Sir Gowland Hopkins, as chairman of the Accessory Food Factors Committee, entrusted this work to Corry Mann.

He carried out his inquiry among boys of a London institution who lived in villas of 30–35 boys each, under comparable housing and domestic conditions. They all had the same basic diet, but to some groups Corry Mann gave an additional pint of pasteurised milk daily. Records were kept of their height, weight, physical fitness, and general health for 1–3 years.

Corry Mann carried out this work with unflagging industry and meticulous care; and in his report, which was published in 1926, he was able to show that the boys whose diet was supplemented with milk gained more weight and grew faster than the controls. Similar experiments by Orr, Leighton, and McKinlay confirmed his findings. The milk-in-school scheme was started by the Board of Education, and by 1934 three million children were receiving milk daily at school. Corry Mann's find-

ings also led to the provision of school dinners on a wider scale and on an adequate scientific basis, and, indirectly, to a revolution in methods of school, domestic, and industrial feeding.

With an established reputation as a nutritional expert, Corry Mann would have liked to give all his efforts to research, but difficulties arose in securing a whole-time appointment, and eventually he returned to consulting practice. He was always regarded as a competent diagnostician and an excellent opinion on diseases of children and their treatment. He retained his interest in his special subject, and in 1935, in our columns,[1] he described an experiment on first-class protein for which he himself was the subject and to which Sir Gowland Hopkins wrote a preface.

In later life he lived chiefly at his club in Pall Mall. He died in Guy's Hospital on Feb. 18.

GEOFFREY JOHN HARRISON

L.R.C.P.I., D.P.M.

Dr. Geoffrey Harrison, medical superintendent of Winwick Hospital, near Warrington, died on Jan. 31 at the age of 54.

Born in Dublin, he was educated at Mountjoy School and qualified in 1929. After holding the post of assistant medical officer at St. Patrick's Hospital, Dublin, he came to Winwick Hospital where he remained till the war. He served in the R.A.M.C. with the rank of major and was mentioned in despatches. His health was affected by his service, but he continued his psychiatric work at Rainhill Hospital and Prestwich Hospital before returning to Winwick in 1948 as deputy medical superintendent. He was appointed medical superintendent in 1953. He leaves a widow and a son. A colleague writes: " Geoff was a sound and capable administrator of absolute integrity held in high regard by his colleagues and well beloved by his patients. He was a friendly, hospitable, and unassuming man who showed a broad humanity from which flowed readily an easy charm and kindness. His later years were marred by continuing ill-health which he bore with exemplary fortitude."

JOHN GERALD EDWARD HAYDEN

C.B.E., M.D.Melb., F.R.C.P., F.R.A.C.P.

Dr. John Hayden, the immediate past president of the Royal Australasian College of Physicians and professor of medicine in the University of Melbourne, died on Dec. 26 at the age of 59 years.

He qualified from the University of Melbourne in 1923, and after holding house-appointments in Melbourne and spending some years of postgraduate study in Europe he settled in consulting practice in Melbourne. He joined the staff of St. Vincent's Hospital and was Stewart lecturer in medicine in the university before he was appointed to his chair. During the late war he served with the Australian Forces in the Middle East and Palestine. He was elected F.R.C.P. in 1941, and he was appointed C.B.E. soon after the end of the war.

T. M. G., his successor in presidential office, writes:

" Dr. John Hayden was an outstanding Melbourne physician. He also had a brilliant war record and will be remembered as consulting physician to the Australian Imperial Forces.

" His connection with the Royal Australasian College of Physicians dates from its foundation in 1938. He had been a member—and a very young member—of the then existing Australasian Association of Physicians. He was among those elected to the first council, now known as the founders, of the college, and he took a leading part in the compilation of its articles and by-laws. He served as a member of the board of censors and later as vice-president and president of the college.

" In a country where private consulting practice is still the order of the day, it is no mean feat to be appointed to a professorial post after the age of 50. The council of the university and his colleagues had no hesitation in appointing him to the professorship of medicine at St. Vincent's Hospital within the University of Melbourne, where it is generally recognised his work was outstanding."

1. *Lancet*, 1935, i, 145.

STEWART ARTHUR SMITH

M.B. Sydney, F.R.C.P., F.R.A.C.P.

Dr. Stewart Smith, director of the medical unit at the Royal Prince Alfred Hospital, Sydney, and a past president of the Royal Australasian College of Physicians, died on Feb. 5.

He was a younger brother of the late Sir Grafton Elliot Smith. He qualified from the University of Sydney in 1903, and after holding resident posts at the Royal Prince Alfred Hospital was appointed to the honorary staff in 1910. He became director of the hospital's medical unit and lecturer in postgraduate medicine in 1938. He held office as treasurer of the Australasian college before he was elected president in 1950. He was also a former chairman of the Australian Rheumatism Council and of the scientific research advisory council of the Life Insurance Medical Research Fund. He was elected to the fellowship of the London college in 1949.

F. B. B. writes:

" S. A. Smith was the kind of man who can make his way to the top in any walk of life, effortlessly and without patronage, through sheer force of character. He was dignified but never pompous. He had a first-class mind, exceptional judgment, and transparent honesty, and he feared no one. He used these qualities to raise standards of medical practice, teaching, and especially research, through the Royal Australasian College of Physicians and, latterly, the Life Insurance Medical Research Fund of Australia and New Zealand, and his work will long outlive him."

Prof. W. MAYER-GROSS

S.K. writes:

" Brilliance in pursuing new paths of research, high purpose in advancing his chosen specialty rather than his status, conciliatory friendliness rising above petty resentment—these are the foundations of the lasting spiritual monument of Willy Mayer-Gross. I remember how in 1927, when I was his subject in a mescaline experiment and when the discomfort of a side-effect troubled me, he took me for a stroll in the park of the psychiatric university clinic of Heidelberg, and did not spare words of encouragement. In 1957, at the Zurich International Congress, he took great care not to leave out any Heidelberger when he convened a friendly gathering around the table in an old Zurich inn. This remarkable gathering, dominated by two men who were the pillars of the whole circle—old Gruhle and Mayer-Gross himself—will, alas, be the last.

" The title of one of the leaders in the issue of *The Lancet* which contained his obituary was Tradition of Excellence. No better motto could be found for Mayer-Gross's life."

Births, Marriages, Deaths

BIRTHS

GELLMAN.—On Feb. 19, at the Winnipeg General Hospital, to Dr. and Mrs. D. D. Gellman, 594, Montrose Street, Winnipeg, 9, Manitoba, a daughter—Catherine Elizabeth.

Notes and News

ANGLO-SOVIET CULTURAL AGREEMENT

A TWO-YEAR Anglo-Soviet agreement on cultural and scientific exchanges was signed in Moscow on Jan. 9.

Cooperation between British and Soviet medical specialists will be fostered. In particular, the U.S.S.R. will send delegations, during the first year, to study chest surgery (3 specialists for four weeks), and virology (3 specialists for three weeks); and, during the second year, one to study the organisation of health services (3 specialists for two weeks), and possibly a second, in communal and industrial hygiene (3 specialists for three weeks).

The U.K. will send 3 specialists to study immunology, and 3 to study experimental medicine, both for three weeks. An equivalent number will be received in the U.S.S.R. in the second year, but their fields of study have not yet been decided.

The exchange of medical films and literature will be encouraged.

Exchanges of scientists will be arranged by the Royal Society and the Academy of Sciences of the U.S.S.R. 4 fellows will go each year to the U.S.S.R. for three weeks to lecture and visit scientific institutions; and 4 academicians or corresponding members of the Academy of Sciences will come to this country. 1 fellow and 1 academician will be exchanged for the longer period of two months. 2 research-workers will spend up to ten months in the other country. In the two-year period of the agreement, 25 British scientists will be invited to the U.S.S.R. to lecture.

In addition other visits of scientists will be arranged on a reciprocal basis.

BUILDING A NEW HOSPITAL

THE lessons learnt in planning, equipping, and bringing into use the Princess Margaret Hospital at Swindon are frankly and objectively discussed in a report [1] published by the Oxford Regional Hospital Board with the support of the Nuffield Provincial Hospitals Trust. Criticisms by patients and staff in the first six months after the opening and details of how orders to the contractor were varied during construction show the importance of planning in the early stages. For instance the basic general services—such as heating, lighting, refrigeration, cleaning, catering, and communication—must be worked out with the architect before pencil is put to paper. Decisions taken, or not taken, at this stage will affect for good or ill all remaining stages, especially the final one when the time comes to occupy the buildings and to work in them.

Planning, building, equipping, and using new buildings are seen as one process and for this reason the report recommends that major capital works should be a joint undertaking by regional hospital boards and hospital management committees, with a small number of senior officers from each authority forming a planning team responsible for coordinating and directing all aspects of each job from start to finish. The report suggests that more staff will be needed to allow some senior officers to give the attention and time that a major project deserves and should receive. Where a new hospital is being started from scratch, the early appointment of key officers will prove a sound investment and, in the long run, an economy.

Not only is planned operational research into hospital design, construction, equipment, and use urgently needed, but the results of such research should be collated and widely read. As Sir George Schuster, the chairman of the board, points out in his foreword, only self-criticism and publication will ensure that public money will be spent to the best advantage. The report comes at a time when hopes for modernising the hospital service are high. It succeeds in showing the opportunity and challenge offered by new hospital building. It also shows the need for fresh thinking and research and for adequate organisation if the new hospital building programme is to be carried through successfully.

A DISTRICT GENERAL HOSPITAL

THE Ministry of Health's latest *Building Notes* include a pattern [2] for a general hospital which recognises "the trend towards the greater integration of the various branches of medicine". It stresses the importance of easy communication between the key diagnostic and treatment department and the wards and outpatient department, and suggests how the departments can be grouped according to zones of activity. But the note is only intended for guidance, for local conditions must be respected and possible future modifications and expansion should not be inhibited by over-rigid planning.

Building Notes nos. 10 and 11 deal with kitchens and dining-rooms respectively.[3]

1. ODDIE, J. A. Commissioning a New Hospital. Oxford Regional Hospital Board (43, Banbury Road, Oxford). 1961. Pp. 263. 10*s*. 6*d*.
2. Building Note no. 3. H.M. Stationery Office. 1961. Pp. 10. 1*s*. 6*d*.
3. Pp. 11. 1*s*. 6*d*.; pp. 4. 1*s*. 3*d*.

University of Oxford

The following degrees have been conferred:

D.M.—Helene V. Goodman, E. H. Jellinek.
M.Ch.—J. H. B. Yule.

University of Cambridge

The degree of M.B. has been conferred on the following:

C. D. M. Drew, *L. D. Heap, R. C. L. Orme, *F. J. B. Taylor, R. W. B. White.

*By proxy.

University of London

Dr. R. A. Shooter, reader in bacteriology at St. Bartholomew's Hospital Medical College, has been appointed to the chair of bacteriology at the college.

Dr. Shooter who is 44 years of age was educated at Mill Hill School, Cambridge University, and St. Bartholomew's Hospital. After qualifying in 1940 he held appointments at Barts, the Royal West Sussex Hospital, and the N.E. London blood-supply depot. He then served in the Royal Navy as surgeon lieutenant R.N.V.R. In 1946 he was appointed lecturer in bacteriology at St. Bartholomew's Hospital Medical College and assistant bacteriologist to the hospital. In 1948 he became senior lecturer and in 1953 reader. During 1950–57 with a Rockefeller travelling fellowship he worked with Dr. Arnold Rich at the Johns Hopkins Hospital. His published work has been mainly about cross-infection in hospital, antibiotics, and cellular nutrition.

Dr. L. H. Hamlyn, lecturer at University College, has been appointed to the university readership in histology at the college, and Dr. J. R. Vane, senior lecturer at the Institute of Basic Medical Sciences, to the university readership in pharmacology at the institute.

University of Aberdeen

Mr. A. G. D. Whyte has been appointed to a lectureship in anatomy, and Dr. Tarunendu Ghose has been awarded a Georgina McRobert research fellowship.

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the Faculty on Feb. 6 with Dr. J. H. Wright, the president, in the chair, the following were admitted to the fellowship:

Ramachandra Eknath Godbole, Mohammed Abdul Mannan, qua physician; Rayik Rifat Abdi, F. J. Collins, F. C. Rodger, qua surgeon.

Faculty of Radiologists

This Faculty is to hold a meeting on Saturday, March 25, in Newcastle upon Tyne. At a joint meeting of the diagnosis and therapy sections the speakers will be Mr. W. M. Ross, Dr. I. B. D. Middlemass, Dr. P. M. Hacking, and Dr. C. K. Warrick.

Wellcome Trust

This Trust has granted £100,000 to the University of Otago, New Zealand, to set up an Institute of Medical Research. Sir Horace Smirk, who is to hold a new chair of research medicine in the university, will develop his research interests at the Institute.

Institute of Hospital Almoners

The annual general meeting of this institute will be held at 5.30 P.M. on Friday, March 17, at the senate house of the University of London, W.C.1, when Miss E. M. Goldberg will speak on the Social Worker in the Sixties.

Chest and Heart Association

This Association is to hold a cardiac symposium on Friday, March 17, at 4.30 P.M. at the Royal College of Physicians of Edinburgh, Queen Street, Edinburgh. Tickets (21*s*.) may be had from the Association, 65, Castle Street, Edinburgh, 2.

Refresher Course in Psychological Medicine

A course of lectures and discussions for general practitioners has been arranged under the auspices of the British Postgraduate Medical Federation by the department of psychological medicine at the Royal Free Hospital. The course will take place over the weekends of April 22 and 23 and May 6 and 7. Further particulars may be had from Dr. Alick Elithorn, Royal Free Hospital, Gray's Inn Road, London, W.C.1.

Life Insurance Medical Research Fund of Australia and New Zealand

This fund has been established to promote and assist scientific and medical research in cardiovascular function and disease. Grants will be made as follows:

Grants in aid (£1000-£3000) will be given to non-profit institutions with basic facilities and qualified personnel for medical research to be used in support of a specific programme of investigation under the direction of a particular investigator.

Research fellowships in Australia and New Zealand (£2220-£2500) will be granted for one year, but renewal for further periods may be approved.

Travelling fellowships (£2500-£3000) will be granted for a period of two years abroad, followed by a third year in an approved institution in Australia or New Zealand.

Further information and application forms, which should be returned by July 1, may be had from Dr. H. M. Whyte, medical director of the fund, 87, Pitt Street, Sydney, New South Wales, Australia.

Gift of Electron Microscope

The National Fund for Research into Poliomyelitis and Other Crippling Diseases has given the Institute of Neurology, National Hospital, Queen Square, London, an electron microscope for research into muscular dystrophy under Prof. J. N. Cumings.

Surgeon Captain H. E. B. Curjel, R.N., has been appointed honorary physician to the Queen in succession to Surgeon Captain T. G. B. Crawford, R.N.

The Earl of Feversham has been appointed chairman of the National Advisory Council on the Employment of the Disabled, in succession to the late Lord Verulam.

Mr. T. Holmes Sellors is to deliver the Walter Wile Hamburger lecture in Chicago on March 6.

On Monday, March 6, at 8.15 P.M., at the Marlborough Day Hospital, 38, Marlborough Place, St. John's Wood, London, N.W.8, Prof. C. A. Mace will give a lecture on the concept of mental health.

A semipermanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, from March 8 to 30, by Dr. A. D. Porter and Dr. I. A. Magnus on effects of light on the skin.

The Empire Rheumatism Council, Faraday House, 8–10, Charing Cross Road, London, W.C.2, has published a handbook for patients on gout. Copies are only available to patients through their doctor.

CORRIGENDA: *Gastrodialysis*.—In this annotation (Jan. 28, p. 211) lines 9 and 8 from the end of the first column should have read: "10-44 mEq. potassium, 24-116 mEq. sodium, 280-480 mEq. chloride, or 0·5-2·3 g. non-protein nitrogen, . . ."

Quadruple Vaccine.—In this annotation (*Lancet*, 1960, ii, 1385) we wrongly stated that Brown and Kendrick (footnote 5) advocated early immunisation of infants with pertussis vaccine alone, followed by administration of a triple vaccine at about 1 year of age.

Appointments

ALDOUS, INEZ R., M.B. Cantab., D.C.H.: assistant county M.O. and school M.O., Aylesbury area.

HORNER, J. S., M.B. Birm., D.P.H., D.I.H.: deputy M.O.H. and deputy school M.O., Dewsbury.

Birmingham Regional Hospital Board:

ANDERSON, W. J. R., M.B. Aberd., M.R.C.O.G., D.OBST.: part-time consultant obstetrician and gynæcologist, Coventry and South Warwickshire hospital groups.

CURRIE, A. B. M., M.B. Glasg., F.R.C.S.E.: consultant surgeon, Birmingham (Selly Oak) hospital group.

LAXTON, G. K., M.B. Leeds, M.R.C.P.E., D.T.M. & H.: consultant physician (geriatrics), Coventry hospital group.

PRICE, J. W., M.B. Aberd., L.D.S.: senior hospital dental officer, Mid-Staffs Mental Hospital and the Stoke-on-Trent hospital group.

SLEE, G. C., M.CH. Orth. Lpool, F.R.C.S.: part-time consultant orthopædic surgeon, Hereford hospital group and the Robert Jones and Agnes Hunt Orthopædic Hospital, Salop.

Diary of the Week

MARCH 5 TO 11

Monday, 6th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. J. F. Goodwin: Defects of Cardiac Septa.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11.30 A.M. (Hammersmith Hospital, Ducane Road, W.12.) Prof. Lee Buxton (Yale): Investigation and Treatment of Primary and Secondary Amenorrhœa. (First of six lectures.)

Tuesday, 7th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Prof. E. P. Sharpey-Schafer: Venous Tone. (First of two Oliver-Sharpey lectures.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. L. W. Proger: Pathology in Hunter's Museum. (Erasmus Wilson demonstration.)

UNIVERSITY OF LONDON
5.30 P.M. (School of Pharmacy, 29, Brunswick Square, W.C.1.) Prof. H. W. Mossman (University of Wisconsin): Glandular Tissues of the Mammalian Ovary.
6 P.M. (University College, Gower Street, W.C.1.) Prof. Charles E. Osgood (University of Illinois): Generalised Model of Behaviour, with Special Reference to Language Functions. (First of three lectures.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. G. P. Lewis: Role of Bradykinin in the Control of Local Blood-flow.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. G. B. Dowling: Collagen Diseases—Scleroderma and Dermatomyositis.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Professor Buxton: Basic Principles of Endocrine Gynæcology. (Second of six lectures.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Prof. C. H. G. Macafee: Placenta Prævia.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. A. D. Gordon: Recent Advances in Neuroradiology.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Prof. Ian Hill: Aspects of Cardiology.

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School.) Prof. D. G. Catcheside: Aspects of Gene Function.

Wednesday, 8th

UNIVERSITY OF LONDON
6 P.M. (University College.) Professor Osgood: Psycholinguistic Relativity versus Universality. (Second of three lectures.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Prof. W. St. C. Symmers: Deep-seated Fungal Infections.

UNIVERSITY COLLEGE LONDON
5.30 P.M. Prof. K. Kramer (University of Göttingen): Renal Blood-flow in Relation to the Counter Current System.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. R. W. Riddell: Epidemiology of Ringworm Infection.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. R. V. Gibson: Management of Atrial and Ventricular Septal Defects.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Prof. A. Vannotti (Lausanne): Metabolism of the Leucocyte.

MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology*. Dr. G. E. Paget: Predictive Pathology.

Thursday, 9th

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Professor Sharpey-Schafer: Venous Tone. (Second of two Oliver-Sharpey lectures.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. R. C. Connolly: Cerebral Ischæmia in Spontaneous Subarachnoid Hæmorrhage. (Hunterian lecture.)

UNIVERSITY OF LONDON
6 P.M. (University College.) Professor Osgood: Cognitive Interaction in Human Affairs. (Last of three lectures.)

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5 P.M. *Ophthalmology*. Dr. D. Maurice, Prof. H. Davson: Corneal Transparency.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. S. C. Gold: Collagen Diseases—Lupus Erythematosus and Polyarteritis Nodosa.

ALFRED ADLER MEDICAL SOCIETY
8 P.M. (11, Chandos Street, W.1.) Dr. Michael Aldridge: Speculations on the Ætiology of Schizophrenia.

MEDICAL ASSOCIATION FOR THE PREVENTION OF WAR
8 P.M. (Friends House, Euston Road, N.W.1.) Dr. W. E. Van Heynigen, Dr. M. C. Berenbaum: Medicine's Unwitting Contribution to War Preparation.

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Mr. Edmund Shephard: Anatomy of Tarsal Movements and its Application in Club Foot.

Friday, 10th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Dr. Basil Morson: Inflammatory Diseases of the Large Intestine with Special Reference to Ulcerative Colitis and Crohn's Disease.
4 P.M. Dr. A. M. Cooke: Mistakes in Medicine.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Mr. Kenneth McLay: Advances in the Study of Cochlear and Vestibular Function.

UNIVERSITY OF ABERDEEN
5 P.M. (Medical School, Foresterhill.) Prof. A. W. Kay: Changing Outlook in the Surgical Treatment of Duodenal Ulceration.